REMARKS

Status of the Claims

The application as filed contained claims 1 – 23. Responsive to a restriction requirement, including species election, applicants have elected to pursue claims 1 – 3, 5 – 12, and 17 – 19. Applicants, therefore, hereby confirm the election of these claims for further prosecution.

The Action has rejected claims 1 – 3, 5 – 12, and 17 – 19 under various statutory grounds. Currently no claims stand allowed. Applicants have added new claims 24 and 25 by amendment herewith. Support for these claims is amply provided in the specification as filed, particularly in Example 3. Consequently, no new matter has been added to the application.

Applicants respectfully submit the following remarks and urge that all of the claims stand in a condition for allowance, which action is respectfully requested.

Objection to Drawings

The Action has indicated an objection to the drawing for Figure 1 on the basis that the legend fro the ordinate access is not legible. Applicants hereby acknowledge said objection and further indicate that, upon receipt of a Notice of Allowance for the instant application, will submit a corrected drawing addressing the noted problem.

Rejections of the Claims

35 U.S.C. §102(b) (Ross *et al.*)

The Action has rejected claims 1-3, 7-9, 12, and 17-19 as allegedly being anticipated by Ross *et al.*, *Pain* **84**: 421-428 (2000) ("Ross"). The Action has characterized Ross as disclosing methods of administering sub-analgesic amounts of morphine and oxycodone followed by an observation of a marked antinociceptive synergy. The Action concluded that "Ross *et al.* intrinsically reduces the risk associated with the administration of opioid analgesics in patients," and reads on the cited claims. Applicants respectfully traverse.

Although the data disclosed in Ross *et al.*, in accord with the Action's characterization, disclose the antinociceptive synergy arising from compositions comprising oxycodone and morphine, it is clear that this result was the sole investigative goal of the work. The reference provides no substantive data on the impact of the synergistic analgesic compositions on expected

side effects such as respiratory depression, which impact is at the core of the invention disclosed and claimed in the instant application. Indeed, the very analgesic synergy disclosed in the Ross *et al.* reference would lead one of ordinary skill in the appropriate art to expect a concomitant level of synergy with respect to side effects of this sort. The widely-accepted reference, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10th Ed., New York: McGraw-Hill (2001) (see copy of Chapter 23, "Opioid Analgesics," attached hereto as Exhibit A) unequivocally states, on page 579, in the context of the use of mixed opioid compositions to reduce the occurrence of side effects such as respiratory depression, that "for the same degree of analgesia, the same intensity of side effects will occur." (Emphasis added.)

The results disclosed in the instant application clearly provide an unexpected benefit from mixed-opioid compositions not predicted by the prior art. The disclosure of Ross *et al.* is directed to the foundation observation that analgesic synergy is possible with compositions comprising mixed μ- and κ-opioid agonists. Any comments directed to possible implications on side effects such as respiratory depression are mere speculation - - speculation, as indicated above, that flies in the face of accepted prior art wisdom. The proof of an unexpected decrease in side effects such as respiratory depression, in a synergistically analgesic mixed-opioid composition, has never been disclosed until the instant application. Thus, the instant application is the first disclosure to establish that it is possible to achieve both analgesia and a reduction in respiratory depression with a composition of mixed μ- and κ-opioid agonists.

The Action, in rejecting claims 1 – 3, 7 – 9, 12, and 17 – 19 over Ross *et al.*, stated that "the method disclosed by Ross et al. intrinsically reduces the risk associated with the administration of opioid analgesics in patients," further citing to disclosed dosing ratios of oxycodone to morphine. Applicants respectfully disagree. To begin with, Applicants point out that the dosing ratios of the compositions for which data is provided in Ross *et al.* do not overlap with those of disclosed and claimed in the instant application, particularly in light of newly added claims 24 and 25. Nor is the mass ratio of one opioid to the other in the composition a minor issue. Looking at extremes of relative loading, even without a clear picture of the mechanism of synergy between the μ- and κ-opioid agonists, it is logical that, as a composition approaches a preponderance of one or the other opioid component, then the opportunity for synergy decreases, until the composition begins to function as if it contains only a single opioid component. Given that each of the single opioid components is present at a sub-analgesic level,

the clinical result would be ineffectiveness for its intended analgesic purpose. Thus, a threshold question arises: what is the minimum ratio of μ- and κ-opioid agonists necessary to create sufficient synergy to achieve the primary analgesic effect? Perhaps more importantly, in terms of the instant invention, is at what relative component ratios is it possible to achieve both analgesic synergy and a reduction in side effects such as respiratory depression?

It is unlikely that data yet exists on where the absolute limits of composition capable of analgesic synergy lie. The disclosure of Ross *et al.* addresses where within those limits analgesically effective compositions may be formulated. However, there is nothing disclosed in the Ross *et al.* reference (or any other reference cited in the Action) on where within those extremes of composition is it possible to achieve both analgesic synergy and a reduction in respiratory depression.

Looking at the specific compositions disclosed in Ross *et al.*, the first route of administration involved intracerebroventricular (i.c.v.) delivery of the compositions directly into the test animal's cerebrospinal fluid *via* a surgically-inserted cannula. The compositions delivered by this route are described as comprising 40 nmol of oxycodone and 15 nmol of morphine, when delivered in combination. Converting these amounts to appropriate mass quantities in grams, based on literature values for the molecular weight of the hydrochloride salts of both active ingredients, the resulting mass ratio of oxycodone to morphine is approximately 2.5:1 (2.464:1). This is a ratio this is substantially beyond that disclosed and claimed in the instant application. However, Applicants point out that this particular route of administration (directly bypassing the blood/brain barrier) significantly affects any observed results from this composition and cannot be, as would be recognized by one of ordinary skill in the relevant art, extrapolated to systemic routes of delivery. The Ross *et al.* reference specifically acknowledges this (see, for example, p. 422).

In looking at the other compositions disclosed in the reference, the relative mass loadings of oxycodone and morphine are considerably different from the instant invention. For intraperitoneal (i.p.) delivery, the compositions comprised 571 nmol of morphine and 621 nmol of oxycodone. Converting to mass units, this represents a 1:1 mass ratio between the components. For subcutaneous (s.c.) delivery, as referenced in the Action, compositions are described in terms of the ED_{50} (providing half maximal response) dose determined from the

individual doses of oxycodone and morphine. Figure 3 of the reference depicts the data on which the authors based this determination. The ED_{50} result was calculated to be 2.8 mg/kg oxycodone and 8.5 mg/kg morphine. Using these figures, relative mass ratios for the compositions administered to the test animals resulted in oxycodone to morphine ratios ranging from 1:9 to 1:1. The mass ratios in these compositions, again, are significantly different from those disclosed and claimed in the instant application. The significance of this difference is emphasized by the recognition in the art (see *Goodman and Gilman's*, attached; Ross *et al.*) that CNS effects such as respiratory depression are mediated through the μ-opioid receptors, those to which morphine binds. If looked to at all for utility in diminishing respiratory depression (counter to then art-accepted principles), the teachings of Ross *et al.* would be undesirable for such effect.

On this basis, Applicants respectfully submit that the cited reference does not adversely impact the patentability of the claims in questions and urges immediate allowance of same.

35 U.S.C. §102(b) (Smith *et al.* WO '438)

The Action has rejected claims 1 – 3, 5, 7 – 12 and 17 – 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* Applicants respectfully traverse.

As addressed above in respect to the disclosures of the Ross *et al.* reference, the disclosure of the Smith *et al.* reference is directed solely to the analgesic synergy arising from compositions comprising mixtures of μ- and κ-opioid agonists. The reference does not disclose any objective data supporting a reduced occurrence of side effects, such as respiratory depression, from administration of the compositions. As also pointed out above, prior to the instant application, the accepted wisdom in the prior art was that any composition displaying an increased analgesic effect would also display an accompanying increase in undesirable side effects (such as respiratory depression). A mere suggestion that it "may be possible" with the disclosed compositions to achieve both analgesia and reduced side effects falls far short of the standard necessary for an anticipating disclosure. As for inherency, contrary to the assertion of the Action, the cited reference fails to disclose any data that would enable one of skill in the art to both recognize and to be able to select from among the wide range of compositions disclosed as displaying analgesic synergy those specific compositions that would also be capable of definitively reducing the occurrence of undesirable side effects such as respiratory depression.

Furthermore, determining the specific mass loadings of the disclosed compositions (see Examples 1 and 4) results in a 2.5:1 oxycodone:morphine ratio for i.c.v. administration, and ratios in the range of 1:9 to 1:1 oxycodone:morphine for systemic administration (see discussion of Ross *et al.*, above). Data from other Examples likewise discloses compositions heavily weighted toward higher morphine:oxycodone mass ratios. These compositions are substantially different from those claimed in the instant application.

Thus, the cited reference provides no objective teaching that the disclosed compositions, in fact, result in reduced side effects, nor do the specific compositions encompass the relative mass loadings of oxycodone and morphine disclosed and claimed in the instant application. On this basis, Applicants respectfully suggest that the cited reference does not adversely impact the patentability of the claims and urges the Examiner to move the application to allowance.

35 U.S.C. §102(b) (Smith *et al.* '072 patent)

The Action has rejected claims 1 – 3, 5, 7 – 12 and 17 – 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* ('072 patent). Applicants respectfully traverse.

As with the Smith *et al.* (WO '438) reference discussed immediately above (which reference is a foreign counterpart to the instant reference and, thus, shares a common disclosure), the cited reference falls far short of anticipating the instant claims. The reference's disclosure is limited solely to the analgesic synergy between μ- and κ-opioid agonists and fails to provide any teaching establishing that the disclosed compositions are capable of reducing the occurrence of side effects such as respiratory depression. Nor does the reference disclose or even suggest how to select from among the numerous compositions disclosed those that would be capable of both providing analgesic synergy and a reduction in undesirable side effects. On this basis, Applicants respectfully submit that the cited fails reference fails to anticipate the instant claims and requests the examiner to withdraw the instant rejection.

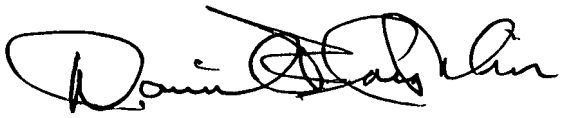
35 U.S.C. §103(a) (Smith *et al.* WO '438)

The Action has rejected claims 1 – 3, 5 – 12 and 17 – 19 under 35 U.S.C. §102(b) as allegedly being anticipated by Smith *et al.* (WO '438). Applicants respectfully traverse.

The Action has cited the reference on the basis that the reference allegedly motivates one of skill in the art to substitute oxymorphone for morphine in the compositions disclosed therein.

Applicants point out that oxymorphone, like morphine, is a μ-opioid agonist. In light of this, the arguments presented above with respect to references disclosing combinations of morphine and oxycodone apply equally well to compositions comprising oxymorphone and oxycodone. Furthermore, as addressed in previous communications with the Examiner in response to earlier-issued restriction requirements, the structural backbone of various opioids and derivatives does not control the physiological properties of such species relevant to the instant invention. Thus, the structural similarity between morphine and oxymorphone, to the extent relevant at all, far from rendering the rejected claims obvious, merely serves to validate the logic of previously proffered arguments directed to morphine compositions disclosed in other cited references. On the basis of structural similarities, there would be no motivation to substitute one μ-opioid agonist for another, at similar mass loadings (adjusted for molecular weight differences) in a composition designed to minimize the side effects known to be regulated through μ-opioid receptors. On this basis, and for the reasons stated above with respect to other bases of rejection, Applicants respectfully submit that the claims as they now stand are patentable over the cited reference and in a condition for allowance. Applicants respectfully request such action.

Respectfully submitted,



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CHAPTER 23

OPIOID ANALGESICS

Howard B. Gutstein and Huda Akil

Opioids have been the mainstay of pain treatment for thousands of years, and remain so today. Opioids exert their therapeutic effects by mimicking the action of endogenous opioid peptides at opioid receptors. Effects on both local neurons and intrinsic pain-modulating circuitry lead to analgesia, other therapeutic effects, and also to undesirable side effects. This chapter will provide the background necessary to understand the mechanisms of action and important pharmacological properties of clinically used opioids. First, the endogenous opioid system is discussed with a focus on the receptors and circuitry utilized by the opioids. A discussion of clinically used compounds follows, describing in detail their pharmacological properties and therapeutic uses. Routes of administration, pain treatment strategies, and current therapeutic guidelines also are presented. This information should provide a rational basis for understanding opioid actions, thereby reducing fear of opioid use and encouraging effective treatment of pain.

OVERVIEW

It is now well known that opioids such as heroin and morphine exert their effects by mimicking naturally occurring substances, termed *endogenous opioid peptides* or *endorphins*. Much now is known about the basic biology of the endogenous opioid system and its molecular and biochemical complexity, widespread anatomy, and diversity. The diverse functions of this system include the best-known sensory role, prominent in inhibiting responses to painful stimuli; a modulatory role in gastrointestinal, endocrine, and autonomic functions; an emotional role, evident in the powerful rewarding and addicting properties of opioids; and a cognitive role in the modulation of learning and memory. The endogenous opioid system is complex and subtle, with a great diversity in endogenous ligands (over a dozen), yet with only four major receptor types. This chapter presents key facts about the biochemical and functional nature of the opioid system. This information then is used to establish a basis for understanding the actions of clinically used opioid drugs and current strategies for pain treatment.

Terminology. The term *opioid* refers broadly to all compounds related to opium. The word *opium* is derived from *opos*, the Greek word for juice, the drug being derived from the juice of the opium poppy, *Papaver somniferum*. *Opiates* are drugs derived from opium, and include the natural products morphine, codeine, thebaine, and many semisynthetic congeners derived from them. *Endogenous opioid peptides* are the naturally occurring ligands for opioid receptors. The term *endorphin* is used synonymously with endogenous opioid peptides, but also refers to a specific endogenous opioid, β-endorphin. The term *narcotic* was derived from the Greek word for stupor. At one time, the term referred to any drug that induced sleep, but then it became associated with opioids. It often is used in a legal context to refer to a variety of substances with abuse or addictive potential.

History. The first undisputed reference to opium is found in the writings of Theophrastus in the third century B.C. Arabian physicians were well versed in the uses of opium; Arabian traders introduced the drug to the Orient, where it was employed mainly for the control of dysenteries. During the Middle Ages, many of the uses of opium were appreciated. In 1680, Sydenham wrote: "Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."

Opium contains more than 20 distinct alkaloids. In 1806, Sertürner reported the isolation of a pure substance in opium that he named morphine, after Morpheus, the Greek god of dreams. The discovery of other alkaloids in opium quickly followed—codeine by Robiquet in 1832, and papaverine by Merck in 1848. By the middle of the nineteenth century, the use of pure alkaloids rather than crude opium preparations began to spread throughout the medical world.

In addition to the remarkable beneficial effects of opioids, the toxic side effects and addictive potential of these drugs also have been known for centuries. These problems stimulated a search for potent, synthetic opioid analgesics free of addictive potential and other side effects. Unfortunately, all of the synthetic compounds that have been introduced into clinical use share the liabilities of classical opioids. However, the search for new opioid agonists led to the synthesis of opioid antagonists and compounds with mixed agonist/antagonist properties, which expanded therapeutic options and provided important tools for exploring mechanisms of opioid actions.

Until the early 1970s, the endogenous opioid system was totally unknown. The actions of morphine, heroin, and other opioids as antinociceptive and addictive agents, while well described, often were studied in the context of interactions with other neurotransmitter systems, such as monoaminergic and cholinergic. Some investigators suggested the existence of a specific opioid receptor because of the unique structural requirements of opiate ligands (Beckett and Casy, 1954), but the presence of an opiate-like system in the brain remained unproven. A particularly misleading observation was that the administration of the opioid antagonist naloxone to a normal animal produced little effect, although the drug was effective in reversing or preventing the effects of exogenous opiates. The first physiological evidence suggesting an endogenous opioid system was the demonstration that analgesia produced by electrical stimulation of certain brain regions was reversed by naloxone (Akil *et al.*, 1972; Akil *et al.*, 1976). Pharmacological evidence for an opiate receptor also was building. In 1973, investigators in three laboratories demonstrated opiate binding sites in the brain (Pert and Snyder, 1973; Simon *et al.*, 1973; Terenius, 1973). This was the first use of radioligand binding assays to demonstrate the presence of membrane-associated neurotransmitter receptors in the brain.

Stimulation-produced analgesia, its naloxone reversibility, and the discovery of opioid receptors strongly pointed to the existence of endogenous opioids. In 1975, Hughes and associates identified an endogenous, opiate-like factor that they called *enkephalin* (from the head) (Hughes *et al.*, 1975). Soon after, two more classes of endogenous opioid peptides were isolated, the *dynorphins* and *endorphins*. Details of these discoveries and the unique properties of the opioid peptides have been reviewed previously (Akil *et al.*, 1984).

Given the large number of endogenous ligands being discovered, it was not surprising that multiple classes of opioid receptors also were found. The concept of opioid-receptor multiplicity arose shortly after the initial demonstration of opiate binding sites. Based on results of *in vivo* studies in dogs, Martin and colleagues postulated the existence of multiple types of opiate receptors (Martin *et al.*, 1976). Receptor-binding studies and subsequent cloning confirmed the existence of three main receptor types, μ, δ, and κ. A fourth member of the opioid peptide receptor family, the *nociceptin/orphanin FQ* (N/OFQ) receptor, was cloned in 1994 (Bunzow *et al.*, 1994; Mollereau *et al.*, 1994). In addition to these four major classes, a number of subtypes have been proposed, such as *epsilon*, often based on bioassays from different species (Schulz *et al.*, 1979); *iota* (Oka, 1980); *lambda* (Grevel and Sadee, 1983); and *zeta* (Zagon *et al.*, 1989). In 2000, the Committee on Receptor Nomenclature and Drug Classification of the International Union of Pharmacology adopted the terms MOP, DOP, and KOP to indicate μ-, δ-, and κ-opioid peptide receptors, respectively. The original Greek letter designation is used in this and other chapters. The Committee also recommended the term NOP for the N/OFQ receptor.

ENDOGENOUS OPIOID PEPTIDES

Three distinct families of classical opioid peptides have been identified: the *enkephalins, endorphins,* and *dynorphins*. Each family is derived from a distinct precursor polypeptide and has a characteristic anatomical distribution. These precursors, preproopiomelanocortin, preproenkephalin, and preprodynorphin, are encoded by three corresponding genes. Each precursor is subject to complex cleavages and posttranslational modifications resulting in the synthesis of multiple active peptides. The opioid peptides share the common amino-terminal sequence of Tyr-Gly-Gly-Phe- (Met or Leu), which has been called the "opioid motif." This motif is followed by various C-terminal extensions yielding peptides ranging from 5 to 31 residues (Table 23–1).

The major opioid peptide derived from proopiomelanocortin (POMC) is β-endorphin. Although β-endorphin contains the sequence for met-enkephalin at its amino terminus, it is not converted to this peptide; met-enkephalin is derived from the processing of preproenkephalin. In addition to β-endorphin, the POMC precursor also is processed into the nonopioid peptides adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (α-MSH), and β-lipotropin (β-LPH). Previous biochemical work (Mains *et al.*, 1977) had suggested a common precursor for the stress hormone ACTH and the opioid peptide β-endorphin. This association implied a close physiological linkage between the stress axis and opioid systems, which was validated by many studies of the phenomenon of stress-induced analgesia (Akil *et al.*, 1986). Proenkephalin contains multiple copies of met-enkephalin as well as a single copy of leu-enkephalin. Prodynorphin contains three peptides of differing lengths that all begin with the leu-enkephalin sequence: dynorphin A, dynorphin B, and neoendorphin (Figure 23–1). The anatomical distribution of these peptides in the central nervous system (CNS) has been reviewed thoroughly by Mansour *et al.* (1988).

A novel endogenous opioid peptide was cloned in 1995 (Meunier *et al.*, 1995; Reinscheid *et al.*, 1995). This peptide has a significant sequence homology to dynorphin A, with an identical length of 17 amino acids, identical carboxy-terminal residues, and a slight modification of the amino-terminal opioid core (Phe-Gly-Gly-Phe instead of Tyr-Gly-Gly-Phe; *see* Table 23–1). The removal of this single hydroxyl group is sufficient to abolish interactions with the three classical opioid-peptide receptors. This peptide was called *orphanin FQ* (OFQ) by one group of investigators and *nociceptin* (N) by another, because it lowered pain threshold under certain conditions. The structure of the N/OFQ precursor (Figure 23–2) suggests that it may encode other biologically active peptides (Nothacker *et al.*, 1996; Pan *et al.*, 1996). Immediately downstream of N/OFQ is a 17-amino-acid peptide (orphanin-2), which also starts with phenylalanine and ends with glutamine but is otherwise distinct from N/OFQ, as well as a putative peptide upstream from N/OFQ, which may be liberated

Table 23–1
Endogenous and Synthetic Opioid Peptides

Selected Endogenous Opioid Peptides	
[Leu^5]enkephalin	**Tyr-Gly-Gly-Phe-Leu**
[Met^5]enkephalin	**Tyr-Gly-Gly-Phe-Met**
Dynorphin A	**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Asp-Asn-Gln
Dynorphin B	**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr
α-Neoendorphin	**Tyr-Gly-Gly-Phe-Leu**-Arg-Lys-Tyr-Pro-Lys
β-Neoendorphin	**Tyr-Gly-Gly-Phe-Leu**-Arg-Lys-Tyr-Pro
β_h-Endorphin	**Tyr-Gly-Gly-Phe-Met**-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
Novel Endogenous Opioid-Related Peptides	
Orphanin FQ/Nociceptin	Phe-**Gly-Gly-Phe**-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln
Endomorphin-1	Tyr-Pro-Trp-Phe
Endomorphin-2	Tyr-Pro-Phe-Phe
Selected Synthetic Opioid Peptides	
DAMGO	[D-Ala^2,MePhe^4,Gly(ol)^5]enkephalin
DPDPE	[D-Pen^2,D-Pen^5]enkephalin
DSLET	[D-Ser^2,Leu^5]enkephalin-Thr^6
DADL	[D-Ala^2,D-Leu^5]enkephalin
CTOP	D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2
FK-33824	[D-Ala^2,N-MePhe^4,Met(O)^5-ol]enkephalin
[D-Ala^2]Deltorphin I	Tyr-D-Ala-Phe-Asp-Val-Val-Gly-NH_2
[D-Ala^2,Glu^4]Deltorphin (Deltorphin II)	Tyr-D-Ala-Phe-Glu-Val-Val-Gly-NH_2
Morphiceptin	Tyr-Pro-Phe-Pro-NH_2
PL-017	Tyr-Pro-MePhe-D-Pro-NH_2
DALCE	[D-Ala^2,Leu^5,Cys^6]enkephalin

upon posttranslational processing (*nocistatin*). The N/OFQ system represents a new neuropeptide system with a high degree of sequence identity to the opioid peptides. However, the slight change in structure results in a profound alteration in function. N/OFQ has behavioral and pain modulatory properties distinct from those of the three classical opioid peptides (*see* below).

The anatomical distribution of POMC-producing cells is relatively limited within the CNS, occurring mainly in the arcuate nucleus and nucleus tractus solitarius. These neurons project widely to limbic and brainstem areas and to the spinal cord (Lewis *et al.*, 1987). There also is evidence of POMC production in the spinal cord (Gutstein *et al.*, 1992). The distribution of POMC corresponds to areas of the human brain where electrical stimulation can relieve pain (Pilcher *et al.*, 1988). Peptides from POMC occur in both the pars intermedia and the pars distalis of the pituitary and also are contained in pancreatic islet cells. The peptides from prodynorphin and proenkephalin are distributed widely throughout the CNS and frequently are found together. Although each family of peptides usually is located in different groups of neurons, occasionally more than one family is expressed within the same neuron (Weihe *et al.*, 1988). Of particular note, proenkephalin peptides are present in areas of the CNS that are presumed to be related to the perception of pain (*e.g.*, laminae I and II of the spinal cord, the spinal trigeminal nucleus, and the periaqueductal gray), to the modulation of affective behavior (*e.g.*, amygdala, hippocampus, locus ceruleus, and the cerebral cortex), to the modulation of motor control (caudate nucleus and globus pallidus), and the regulation of the autonomic nervous system (medulla oblongata) and neuroendocrinological functions (median eminence). Although there are a few long enkephalinergic fiber tracts, these peptides are contained primarily in interneurons with short axons. The peptides from proenkephalin also are found in the adrenal medulla and in nerve plexuses and exocrine glands of the stomach and intestine.

The N/OFQ precursor has a unique anatomical distribution (Neal *et al.*, 1999b). The distribution of this system suggests

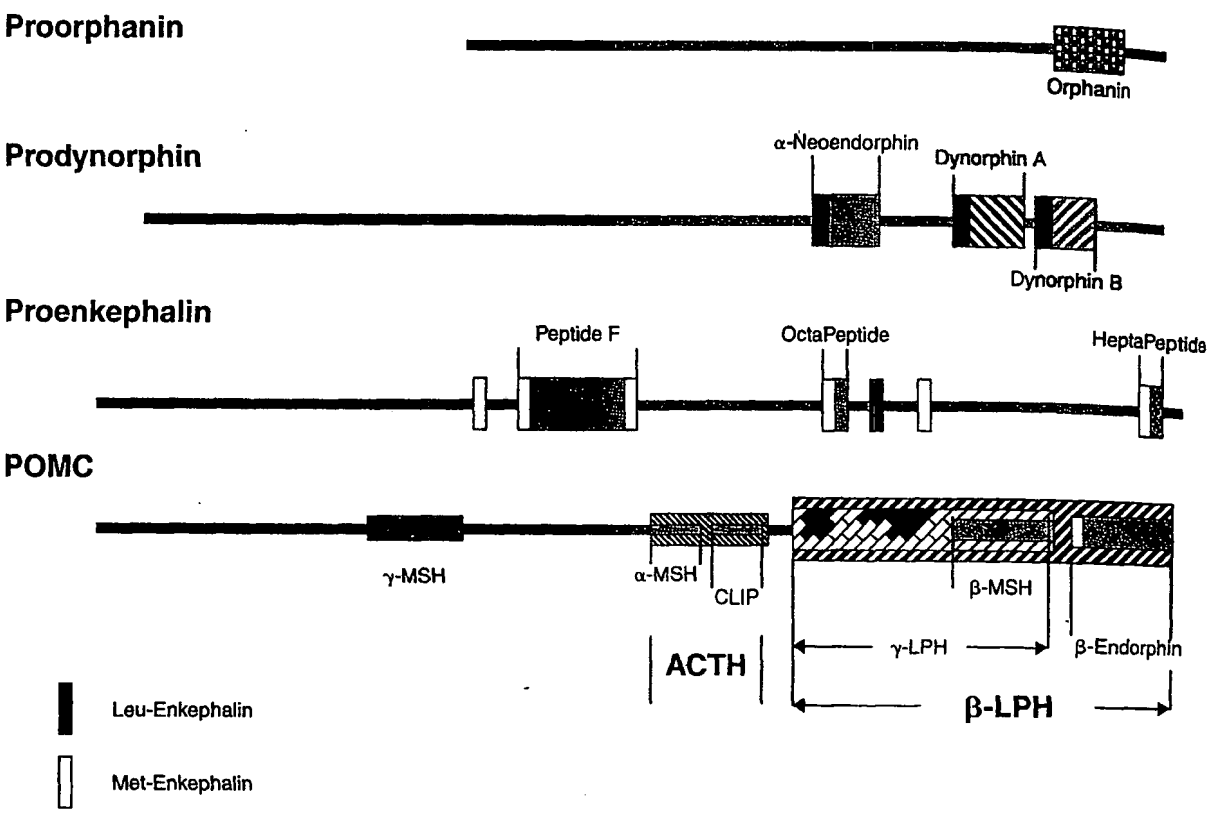
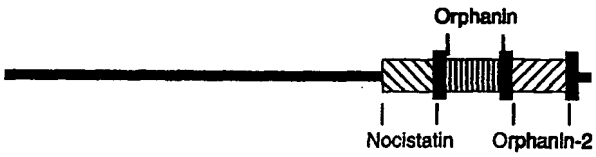


Figure 23–1. Peptide precursors. (From Akil et al., *1998.)*
POMC, proopiomelanocortin; ACTH, adrenocorticotropic hormone; β-LPH, β-lipotropin.

important roles in hippocampus, cortex, and numerous sensory sites. N/OFQ produces a complex behavioral profile, including effects on drug reward and reinforcement (Bertorelli *et al.*, 2000; Devine *et al.*, 1996a; Devine *et al.*, 1996b), stress responsiveness (Devine *et al.*, 2001; Koster *et al.*, 1999), and learning and memory processes (Koster *et al.*, 1999; Manabe *et al.*, 1998). Studies of the effect of N/OFQ on pain sensitivity have produced conflicting results, which may be reconciled by data suggesting that the effects of N/OFQ on pain sensitivity depend on the underlying behavioral state of the animal (Pan *et al.*, 2000) (*see* below). Analogous mechanisms also could explain some of the conflicting results with other physiological processes. However, more studies are needed before a general role can be ascribed to the N/OFQ system, including the investigation of other active peptides that may be derived from the N/OFQ precursor (Figure 23–2). Nocistatin has been tested behaviorally and found to produce effects opposite to those of N/OFQ (Okuda-Ashitaka *et al.*, 1998). In sum, these findings, coupled with the extensive anatomy of the system, suggest that the N/OFQ precursor plays a complex role in the brain that is yet to be fully appreciated.



110-127 Nocistatin	MPRVRSLFQEQEEPEPGMEEAGEMEQKQLQ
130-146 Orphanin	FQFGGFTGARKSARKLANQ
149-165 Orphanin-2	FSEFMRQYLVLSMQSSQ

Figure 23–2. Human proorphanin-derived peptides.

Not all cells that make a given precursor polypeptide store and release the same mixture of active opioid peptides, because of differential processing secondary to variations in the cellular complement of peptidases that produce and degrade the active opioid fragments (Akil *et al.*, 1984). In addition, processing of these peptides is altered by physiological demands, leading to a different mix of peptides being released by the same cell under different conditions. For example, chronic morphine treatment (Bronstein *et al.*, 1990) or stress (Akil *et al.*, 1985) can alter the forms of β-endorphin released by cells, which could possibly underlie some observed physiological adaptations. Although the endogenous opioid peptides appear to function as neurotransmitters, modulators of neurotransmission, or neurohormones, the full extent of their physiological role is not completely understood (Akil *et al.*, 1988). The elucidation of

the physiological roles of the opioid peptides has been made more difficult by their frequent coexistence with other putative neurotransmitters within a given neuron.

OPIOID RECEPTORS

Three classical opioid receptor types, μ, δ, and κ, have been studied extensively. The more recently discovered N/OFQ receptor, initially called the opioid-receptor-like 1 (ORL-1) receptor or "orphan" opioid receptor has added a new dimension to the study of opioids. Highly selective ligands that allowed for type-specific labeling of the three classical opioid receptors (*e.g.*, DAMGO for μ, DPDPE for δ, and U-50,488 and U-69,593 for κ) (Handa *et al.*, 1981; Mosberg *et al.*, 1983; Voightlander *et al.*, 1983) became available in the early 1980s. These tools made possible the definition of ligand-binding characteristics of each of the receptor types and the determination of anatomical distribution of the receptors using autoradiographic techniques. Each major opioid receptor has a unique anatomical distribution in brain, spinal cord, and the periphery (Mansour *et al.*, 1988; Neal *et al.*, 1999b). These distinctive patterns of localization suggested possible functions that subsequently have been investigated in pharmacological and behavioral studies.

The study of the biological functions of opioid receptors *in vivo* was aided by the synthesis of selective antagonists and agonists. Among the most commonly used antagonists are cyclic analogs of somatostatin such as CTOP as μ-receptor antagonists, a derivative of naloxone called naltrindole as a δ-receptor antagonist, and a bivalent derivative of naltrexone called binaltorphimine (nor-BNI) as a κ-receptor antagonist (Gulya *et al.*, 1986; Portoghese *et al.*, 1987; Portoghese *et al.*, 1988). In general, functional studies using selective agonists and antagonists have revealed substantial parallels between μ and δ receptors and dramatic contrasts between μ/δ and κ receptors. *In vivo* infusions of selective antagonists and agonists also were used to establish the receptor types involved in mediating various opioid effects (Table 23–2).

Most of the clinically used opioids are relatively selective for μ receptors, reflecting their similarity to morphine

Table 23–2
Classification of Opioid Receptor Subtypes and Actions from Animal Models

	RECEPTOR SUBTYPE	ACTIONS OF: AGONISTS	ANTAGONISTS
Analgesia			
Supraspinal	μ, κ, δ	Analgesic	No effect
Spinal	μ, κ, δ	Analgesic	No effect
Respiratory function	μ	Decrease	No effect
Gastrointestinal tract	μ, κ	Decrease transit	No effect
Psychotomimesis	κ	Increase	No effect
Feeding	μ, κ, δ	Increase feeding	Decrease feeding
Sedation	μ, κ	Increase	No effect
Diuresis	κ	Increase	
Hormone regulation			
Prolactin	μ	Increase release	Decrease release
Growth hormone	μ and/or δ	Increase release	Decrease release
Neurotransmitter release			
Acetylcholine	μ	Inhibit	
Dopamine	μ, δ	Inhibit	
Isolated organ bioassays			
Guinea pig ileum	μ	Decrease contraction	No effect
Mouse vas deferens	δ	Decrease contraction	No effect

The actions listed for antagonists are seen with the antagonist alone. All the correlations in this table are based on studies in rats and mice, which occasionally show species differences. Thus, any extensions of these associations to human beings are tentative. Clinical studies do indicate that μ receptors elicit analgesia both spinally and supraspinally. Preliminary work with a synthetic opioid peptide, [D-Ala^2,D-Leu^5]enkephalin, suggests that intrathecal δ agonists are analgesic in human beings.

SOURCE: Modified from Pasternak (1993).

Table 23–3
Actions and Selectivities of Some Opioids at the Various Opioid Receptor Classes

	RECEPTOR TYPES		
	μ	δ	κ
Drugs			
Morphine	+++		+
Methadone	+++		
Etorphine	+++	+++	+++
Levorphanol	+++		
Fentanyl	+++		
Sufentanil	+++	+	+
DAMGO	+++		
Butorphanol	P		+++
Buprenorphine	P		−−
Naloxone	−−−	−	−−
Naltrexone	−−−	−	−−−
CTOP	−−−		
Diprenorphine	−−−	−−	−−−
β-Funaltrexamine	−−−	−	++
Naloxonazine	−−−	−	−
Nalorphine	−−−		+
Pentazocine	P		++
Nalbuphine	−−		++
Naloxone benzoylhydrazone	−−−	−	−
Bremazocine	+++	++	+++
Ethylketocyclazocine	P	+	+++
U50,488			+++
U69,593			+++
Spiradoline	+		+++
nor-Binaltorphimine	−	−	−−−
Naltrindole	−	−−−	−
DPDPE		++	
[D-Ala^2,Glu^4]deltorphin		++	
DSLET	+	++	
Endogenous Peptides			
Met-enkephalin	++	+++	
Leu-enkephalin	++	+++	
β-Endorphin	+++	+++	
Dynorphin A	++		+++
Dynorphin B	+	+	+++
α-Neoendorphin	+	+	+++

Activities of drugs are given at the receptors for which the agent has reasonable affinity. +, agonist: −, antagonist: P, partial agonist: DAMGO, CTOP, DPDPE, DSLET, *see* Table 23–1. The number of symbols is an indication of potency: the ratio for a given drug denotes selectivity. These values were obtained primarily from animal studies and should be extrapolated to human beings with caution. Both β-funaltrexamine and naloxonazine are irreversible μ antagonists, but β-funaltrexamine also has reversible κ agonist activity.

Table 23–4
Properties of the Cloned Opioid Receptors

RECEPTOR SUBTYPE	SELECTIVE LIGANDS		NONSELECTIVE LIGANDS		PUTATIVE ENDOGENOUS LIGANDS
	Agonists	*Antagonists*	*Agonists*	*Antagonists*	
μ	DAMGO Morphine Methadone Fentanyl Dermorphin	CTOP	Levorphanol Etorphine	Naloxone Naltrexone β-Funaltrexamine	Enkephalin Endorphin
κ	Spiradoline U50,488 Dynorphin A	Nor-BNI	Levorphanol Etorphine EKC	Naloxone Naltrexone	Dynorphin A
δ	DPDPE Deltorphin DSLET	Naltrindole NTB BNTX	Levorphanol Etorphine	Naloxone Naltrexone	Enkephalin

ABBREVIATIONS: BNTX, 7 benzylidenenaltroxone; EKC, ethylketocyclazosine NTB, benzofuran analog of naltrindole; nor-BNI, nor-binaltorphimine. DAMGO, CTOR, DPDPE, DSLET, *see* Table 23–1.
SOURCE: Modified from Raynor *et al.* (1994).

(Tables 23–3 and 23–4). However, it is important to note that drugs that are relatively selective at standard doses will interact with additional receptor subtypes when given at sufficiently high doses, leading to possible changes in their pharmacological profile. This is especially true as doses are escalated to overcome tolerance. Some drugs, particularly mixed agonist-antagonist agents, interact with more than one receptor class at usual clinical doses. The actions of these drugs are particularly interesting, since they may act as an agonist at one receptor and an antagonist at another.

There is little agreement regarding the exact classification of opioid receptor subtypes. Pharmacological studies have suggested the existence of multiple subtypes of each receptor. The complex literature on κ opioid-receptor subtypes (*see* Akil and Watson, 1994) strongly suggests the presence of at least one additional subtype with good affinity for the benzomorphan class of opiate alkaloids. The data for δ-opioid receptor subtypes is intriguing. While early support for the possibility of multiple δ receptors came from radioligand-binding studies (Negri *et al.*, 1991), the strongest evidence derives from behavioral studies (Jiang *et al.*, 1991; Sofuoglu *et al.*, 1991), which led to the proposal that two δ-receptor sites exist, δ_1 and δ_2. In the case of the μ receptor, behavioral and pharmacological studies led to the proposal of μ_1 and μ_2 subtypes (Pasternak, 1986). The μ_1 site is proposed to be a very high affinity receptor with little discrimination between μ and δ ligands. A parallel hypothesis (Rothman *et al.*, 1988) holds that there is a high affinity μ/δ complex rather than a distinct μ site. Although molecular cloning studies have not readily supported the existence of these subtypes as distinct molecules, recent findings (*see* below) regarding modified specificity for opioid ligands due to heterodimerization of receptors may provide an explanation for observed pharmacological diversity (Jordan and Devi, 1999).

Molecular Studies of Opioid Receptors and Their Ligands

For many years, the study of multiple opioid receptors greatly profited from the availability of a rich array of natural and synthetic ligands but was limited by the absence of opioid receptor clones. In 1992, the mouse δ receptor was cloned from the NG-108 cell line (Evans *et al.*, 1992; Kieffer *et al.*, 1992). Subsequently, the other two major types of classical opioid receptors were cloned from various rodent species (Chen *et al.*, 1993; Kong *et al.*, 1994; Meng *et al.*, 1993; Minami *et al.*, 1993; Thompson *et al.*, 1993; Wang *et al.*, 1993; Yasuda *et al.*, 1993). The N/OFQ receptor was cloned as a result of searches for novel types or subtypes of opioid receptors. The coding regions for the opioid-peptide receptors subsequently were isolated and chromosomally assigned (Befort *et al.*, 1994; Yasuda *et al.*, 1994; Wang *et al.*, 1994). In the case of μ, the cloned sequence is the classical morphine-like receptor, rather than the proposed μ_1. With δ, no differentiation between the two proposed types by binding appears possible, and the cloned receptor recognizes all δ-selective ligands regardless of their behavioral assignment as δ_1 or δ_2. For κ, the cloned receptor is the classical receptor, rather than the proposed benzomorphan binding site. All four opioid receptors belong to the G protein-coupled receptor (GPCR) family (*see* Chapter 2) and share extensive sequence homologies (Figure 23–3). The N/OFQ receptor has high structural homology with the classical opioid receptors, but it has very low or no affinity for binding conventional opioid ligands (Bunzow *et al.*, 1994; Chen *et al.*, 1994; Mollereau *et al.*, 1994).

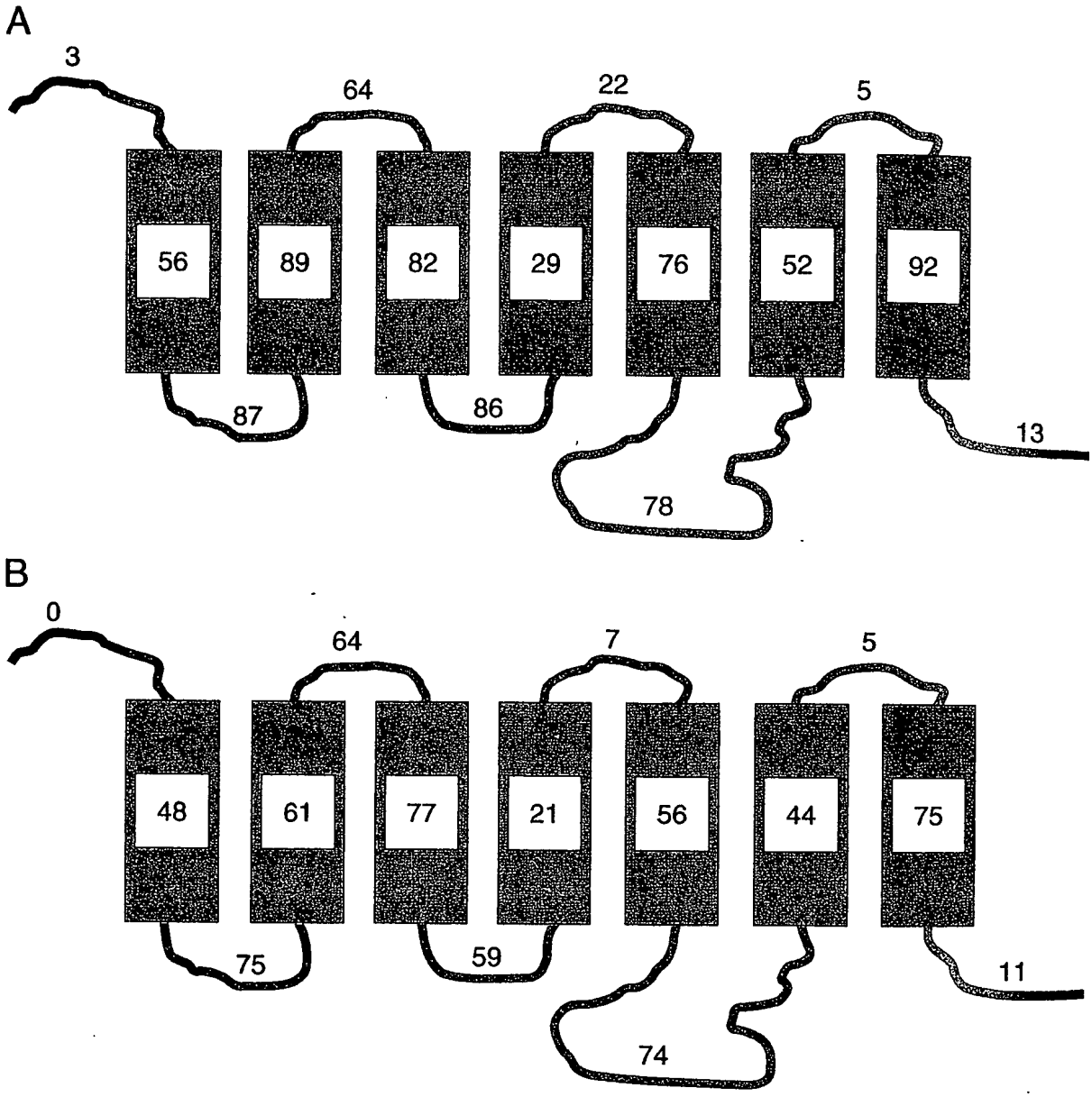


Figure 23–3. A. Structural homology among the three opioid receptors. B. Structural homology among the three opioid receptors and the N/OFQ receptor. *(From Akil* et al., *1998, with permission.)* Numbers indicate the percent of identical amino acids in the segment.

The structural similarities of the N/OFQ receptor and the three classical opioid receptors are highest in the transmembrane regions and cytoplasmic domains and lowest in the extracellular domains critical for ligand selectivity (Figure 23–3B).

It is possible that further cloning experiments may identify unique genes encoding opioid receptor subtypes. However, it has been suggested that, if multiple opioid receptor subtypes exist, they could be derived from a single gene, and multiple mechanisms might exist to achieve distinct pharmacological profiles. Two potential pathways to opioid receptor diversity are alternative splicing of receptor RNA and dimerization of receptor proteins.

Alternative splicing of receptor heteronuclear RNA (*e.g.*, exon skipping and intron retention) is thought to play an

important role in producing *in vivo* diversity within many members of the GPCR superfamily (Kilpatrick *et al.*, 1999). Splice variants may exist within each of the three opioid receptor families, and this alternative splicing of receptor transcripts may be critical for the diversity of opioid receptors. A technique widely used to identify potential sites of alternative splicing is antisense oligodeoxynucleotide (ODN) mapping. The ability of antisense ODNs to target specific regions of cDNA permits the systematic evaluation of the contribution of individual exons to observed receptor properties. Antisense ODN-targeting of exon 1 of the rat and mouse μ opioid receptors blocks morphine analgesia in these species (Rossi *et al.*, 1995; Rossi *et al.*, 1996a; Rossi *et al.*, 1997). By contrast, administration of antisense ODNs targeting exon 2 does not block morphine analgesia but prevents the analgesia produced by heroin, fentanyl, and the morphine metabolite morphine-6-glucuronide (Rossi *et al.*, 1995; Rossi *et al.*, 1996a; Rossi *et al.*, 1997). An analogous disruption of morphine-6-glucuronide–induced but not morphine-induced analgesia is observed following administration of antisense ODNs targeting exon 3 (Rossi *et al.*, 1997). These results imply that unique μ receptor mechanisms mediate the analgesic effects of a variety of opioids and are consistent with the claim that these unique receptor mechanisms could be achieved *via* alternative splicing. The use of antisense ODNs also has led to the identification of potential sites for splice variation in the κ- and δ-opioid receptors (Pasternak and Standifer, 1995). Central to the claim that these results reflect the existence of splice variants is the *in vivo* isolation of such variants. A μ-opioid receptor splice variant has been identified that differs considerably from the native receptor within its C-terminus (Zimprich *et al.*, 1995). As might be expected on the basis of the splicing location, this variant exhibits a binding profile similar to that of the cloned μ-opioid receptor but does not readily undergo the desensitization frequently observed following exposure to agonist. Thus, the existence of this splice variant cannot explain the differential analgesic sensitivities described above. However, just such a variant was detected in mice with a targeted disruption of exon 1 (Schuller *et al.*, 1999). Transcripts of the μ-opioid receptor that contained exons 2 and 3 were identified in these mice. Moreover, whereas morphine-induced analgesia was abolished, heroin- and M6G-induced analgesia were unaffected.

The interaction of two receptors to form a unique structure (dimerization) also has been accorded an important role in regulating receptor function. For example, dimerization of $GABA_{BR1}$ and $GABA_{BR2}$ subunits is required to form a functional $GABA_B$ receptor for gamma-aminobutyric acid (*e.g.*, Jones *et al.*, 1998). Both cloned κ- and δ-opioid receptors have been shown to exist *in vitro* as homodimers (Cvejic and Devi, 1997). However, the most interesting findings have been generated by studies showing dimerization between different opioid receptor types. Jordan and Devi (1999) showed that κ- and δ-opioid receptors can exist as heterodimers both in heterologous expression systems and in brain, based on coimmunoprecipitation studies. The dimerization of these receptors profoundly alters their pharmacological properties. The affinity of the heterodimers for highly selective agonists and antagonists is greatly reduced. Instead, the heterodimers show greatest affinity for partially selective agonists such as bremazocine, suggesting that receptor hetero dimerization may explain at least part of the discrepancy between molecular and pharmacological properties of opioid receptors.

Given the existence of four families of endogenous ligands and cloned receptors, it seems reasonable to ask if there is a one-to-one correspondence between them. Previous studies using brain homogenates demonstrated that an orderly pattern of association between a set of opioid gene products and a given receptor does not exist. Although proenkephalin products generally are associated with δ and prodynorphin products with κ receptors, much "cross-talk" is present (Mansour *et al.*, 1995). The cloning of the opioid receptors allowed this question to be addressed more systematically, since each receptor could be expressed separately and then compared side by side under identical conditions (Mansour *et al.*, 1997). The κ receptor exhibits the most selectivity across endogenous ligands, with affinities ranging from 0.1 nM for dynorphin A to approximately 100 nM for leu-enkephalin. In contrast, μ and δ receptors show only a 10-fold difference between the most- and least-preferred ligand, with a majority of endogenous ligands exhibiting greater affinity for δ than for μ receptors. The limited selectivity of μ and δ receptors suggests that the μ and δ receptor recognize principally the Tyr-Gly-Gly-Phe core of the endogenous peptide, whereas the κ receptor requires this core *and* the arginine in position 6 of dynorphin A and other prodynorphin products (*see* Table 23–1). Interestingly, proenkephalin products with arginine in position 6 (*i.e.*, met-enkephalin-Arg-Phe and met-enkephalin-Arg-Gly-Leu) are equally good κ-receptor ligands, arguing against the idea of a unique association between a given receptor and a given opioid precursor family. In sum, high affinity interactions are possible between each of the peptide precursor families and each of the three receptor types, the only exception being the lack of high-affinity interaction between POMC-derived peptides and κ receptors. Otherwise, at least one peptide product from each of the families exhibits high affinity (low nanomolar or subnanomolar) for each receptor. The relatively unimpressive affinity of the μ receptor toward all known endogenous ligands suggests that its most avid and selective ligand has not been identified, a notion being put to test (*see* below).

Endomorphins. The search for a high affinity/high selectivity endogenous ligand for the μ receptor led to the discovery of a class of novel endogenous opioids termed *endomorphins* (Zadina *et al.*, 1997). Endomorphin-1 and endomorphin-2 are tetrapeptides with the sequences Tyr-Pro-Trp-Phe and Tyr-Pro-Phe-Phe, respectively (Table 23–1). These novel peptides do not contain the canonical opioid core (Tyr-Gly-Gly-Phe) but nevertheless bind the μ receptor with very high affinity and selectivity. However, an endomorphin gene has yet to be cloned, and much remains to be learned about the endomorphins' anatomical distribution, mode of interaction with the opioid receptors, function *in vivo*, and the potential existence of other related peptides that are highly selective for each of the opioid receptors.

Molecular Basis for Opioid Receptor Selectivity and Affinity. Previous studies of other peptide receptors suggested that peptides and small molecules may bind to GPCRs differently. Mutagenesis studies of small ligand receptors (*e.g.*, adrenergic and dopamine receptors) showed that charged amino acid residues in the transmembrane domains were important in receptor binding and activation (Strader *et al.*, 1988; Mansour *et al.*, 1992). This observation places the bound ligands within

the receptor core formed by the transmembrane helices. On the other hand, studies with peptidergic receptors have demonstrated a critical role for extracellular loops in ligand recognition (Xie *et al.*, 1990). All three classical opioid receptors appear to combine both properties: Charged residues located in transmembrane domains have been implicated in the high affinity binding of most opioid ligands, whether alkaloid or peptide (Surratt *et al.*, 1994; Mansour *et al.*, 1997). However, critical interactions of opioid peptides with the extracellular domains also have been shown.

The opioid peptide Tyr-Gly-Gly-Phe core, sometimes termed the "message," appears to be necessary for interaction with the receptor-binding pocket; however, peptide *selectivity* resides in the carboxy-terminal extension beyond the tetrapeptide core, providing the "address" (Schwyzer, 1986). When the carboxy-terminal domain is long, it may interact with extracellular loops of the receptors, contributing to selectivity in a way that cannot be achieved by the much smaller alkaloids. Indeed, dynorphin A selectivity is dependent on the second extracellular loop of the κ receptor (Kong *et al.*, 1994; Xue *et al.*, 1994; Meng *et al.*, 1995), whereas δ- and μ-selective ligands have more complex mechanisms of selectivity that depend on multiple extracellular loops. These findings have led to the proposal that high selectivity is achieved by both attraction to the most-favored receptor and repulsion by the less-favored receptor (Watson *et al.*, 1995; Meng *et al.*, 1995). For example, the N/OFQ receptor does not bind any of the classical endogenous opioid peptides. However, mutating as few as four amino acids endows the N/OFQ receptor with the ability to recognize prodynorphin-derived peptides while retaining recognition of N/OFQ (Meng *et al.*, 1996), suggesting that unique mechanisms have evolved to ensure selectivity of the N/OFQ receptor for N/OFQ and against classical opioid peptides. Mechanisms involved in selectivity can be difficult to separate from mechanisms involved in affinity, because the extracellular domains may not only allow interactions with the peptide ligands but also may be important in stabilizing these interactions.

Results of the research discussed above imply that the alkaloids are small enough to fit completely inside or near the mouth of the receptor core, while peptides bind to the extracellular loops and simultaneously extend to the receptor core to activate the common binding site. That one can truly separate the binding of peptides and alkaloids is demonstrated most clearly by a genetically engineered κ receptor (Coward *et al.*, 1998), which does not recognize endogenous peptide ligands, yet retains full affinity and efficacy for small synthetic κ-receptor ligands, such as spiradoline. Given these differences in binding interactions with the receptor, it is possible that unique classes of ligands may activate the opioid receptor differently, leading to conformational changes of distinct quality or duration that may result in varying magnitudes and possibly different second-messenger events. This hypothesis currently is being tested and, if validated, may lead to novel strategies for differentially altering the interactions between the opioid receptors and signal transduction cascades. With the potential presence of receptor heterodimers and the likelihood that they have unique profiles and signaling properties (Jordan and Devi, 1999), there now are a number of new directions for discovery of drugs that may target receptors in particular states.

Opioid Receptor Signaling and Consequent Intracellular Events

Coupling of Opioid Receptors to Second Messengers. The μ, δ, and κ receptors in endogenous neuronal settings are coupled, *via* pertussis toxin-sensitive GTP-binding proteins, to inhibition of adenylyl cyclase activity (Herz, 1993), activation of receptor-operated K^+ currents, and suppression of voltage-gated Ca^{2+} currents (Duggan and North, 1983). The hyperpolarization of the membrane potential by K^+-current activation and the limiting of Ca^{2+} entry by suppression of Ca^{2+} currents are tenable but unproven mechanisms for explaining blockade by opioids of neurotransmitter release and pain transmission in varying neuronal pathways. Studies with cloned receptors have shown that opioid receptors may couple to an array of other second messenger systems, including activation of the MAP kinases and the phospholipase C (PLC)-mediated cascade leading to the formation of inositol trisphosphate and diacylglycerol (*see* Akil *et al.*, 1997, for review). Prolonged exposure to opioids results in adaptations at multiple levels within these signaling cascades. The significance of these cellular-level adaptations lies in the causal relationship that may exist between them and adaptations seen at the organismic level such as tolerance, sensitization, and withdrawal.

Receptor Desensitization, Internalization, and Sequestration Following Chronic Exposure to Opioids. Transient administration of opioids leads to a phenomenon termed *acute tolerance*, whereas sustained administration leads to the development of "classical" or *chronic tolerance. Tolerance* simply refers to a decrease in effectiveness of a drug with its repeated administration. Recent studies have focused on cellular mechanisms of acute tolerance. Several investigators have shown that short-term desensitization probably involves phosphorylation of the μ and δ receptors *via* protein kinase C (Mestek *et al.*, 1995; Narita *et al.*, 1995; Ueda *et al.*, 1995). A number of other kinases also have been implicated, including protein kinase A and β-adrenergic receptor kinase, βARK (Pei *et al.*, 1995; Wang *et al.*, 1994; also, *see* below).

Like other GPCRs, both μ and δ receptors can undergo rapid agonist-mediated internalization *via* a classic endocytic pathway (Trapaidze *et al.*, 1996; Gaudriault *et al.*, 1997), whereas κ receptors do not internalize following prolonged agonist exposure (Chu *et al.*, 1997). Interestingly, it seems that internalization occurs *via* partially distinct endocytic pathways for the μ and δ receptors, suggesting *receptor*-specific interactions with different mediators of intracellular trafficking (Gaudriault *et al.*, 1997). It also is intriguing that these processes may be induced differentially as a function of the structure of the *ligand.* For example, certain agonists, such as etorphine and enkephalins, cause rapid internalization of the μ receptor, while morphine, although it decreases adenylyl cyclase activity equally well, does not cause μ receptor internalization (Keith *et al.*, 1996). In addition, a truncated μ receptor with normal G protein coupling was shown to recycle constitutively from the membrane to cytosol (Segredo *et al.*, 1997), further indicating that activation of signal transduction and internalization are controlled by distinct molecular mechanisms. These studies also support the hypothesis that different ligands induce different conformational changes in the

receptor that result in divergent intracellular events, and they may provide an explanation for differences in the efficacy and abuse potential of various opioids. One of the most interesting studies to evaluate the relevance of these alterations in signaling to the adaptations seen in response to opioid exposure *in vivo* was the demonstration that acute morphine-induced analgesia was enhanced in mice lacking β-arrestin 2 (Bohn *et al.*, 1999). Opioid-receptor internalization is mediated, at least partially, by the actions of GPCR kinases (GRKs). GRKs selectively phosphorylate agonist-bound receptors, thereby promoting interactions with β-arrestins, which interfere with G protein coupling and promote receptor internalization (Bohn *et al.*, 1999). Enhanced analgesia in mice lacking β-arrestin 2 is consistent with a role for the GRKs and arrestins in regulating responsivity to opioids *in vivo*. This result is even more intriguing given the inability of morphine to support arrestin translocation and receptor internalization *in vitro* (Whistler and von Zastrow, 1998).

Traditionally, long-term tolerance has been thought to be associated with increases in adenylyl cyclase activity—a counterregulation to the decrease in cyclic AMP levels seen after acute opioid administration (Sharma *et al.*, 1977). Chronic treatment with μ-receptor opioids causes superactivation of adenylyl cyclase (Avidor-Reiss *et al.*, 1996). This effect is prevented by pretreatment with pertussis toxin, demonstrating involvement of $G_{i/o}$ proteins, and also by cotransfection with scavengers of G protein-$\beta\gamma$ dimers, indicating a role for this complex in superactivation. Alterations in levels of cyclic AMP clearly bring about numerous secondary changes (*see* Nestler and Aghajanian, 1997).

An "Apparent Paradox." A paradox in evaluating the function of endogenous opioid systems is that a host of endogenous ligands activate a small number of opioid receptors. This pattern is different from that of many other neurotransmitter systems, where a single ligand interacts with a large number of receptors having different structures and second messengers. Is this richness and complexity at the presynaptic level lost as multiple opioid ligands derived from different genes converge on only three receptors, or is this richness preserved through means yet to be discovered? One possibility is that all opioid receptors have not been revealed by molecular cloning. Other options include splice variants, dimerization, and posttranslational modification, as discussed previously. Even assuming that other receptors and variants will be found, the binding of many endogenous ligands to the three cloned classical receptors suggests a great deal of convergence. However, this convergence may be only apparent, since multiple mechanisms for achieving distinctive responses in the context of the biology described above may exist. Some issues to consider are as follows:

1. The *duration of action* of endogenous ligands may be a critical variable that has been overlooked and that may have clinical relevance.
2. The *pattern or profile of activation of multiple receptors by a ligand,* rather than activation of a single receptor, may be a critical determinant of effect.
3. *Opioid genes may give rise to multiple active peptides with unique profiles of activity.* This patterning may be very complex and regulatable by various stimuli.
4. *Patterns and/or efficacy of intracellular signaling* produced by endogenous ligands at opioid receptors are under investigation (Emmerson *et al.*, 1996). This issue may be particularly relevant for understanding physiological alterations following chronic administration of exogenous opioids.
5. *Intracellular trafficking of the receptors* may vary both as a function of the receptor and the ligand. This could have interesting implications for long-term adaptations during sustained treatment with opioids and following their withdrawal.

Understanding the complexity of endogenous opioid peptides and their patterns of interaction with multiple opioid receptors may help define the similarities and differences between the endogenous modulation of these systems and their activation by drugs. These insights could be important in devising treatment strategies that maximize beneficial properties of opioids (*e.g.*, pain relief) while limiting their undesirable side effects such as tolerance, dependence, and addiction.

EFFECTS OF CLINICALLY USED OPIOIDS

Morphine and most other clinically used opioid agonists exert their effects through μ opioid receptors. These drugs affect a wide range of physiological systems. They produce analgesia, affect mood and rewarding behavior (*see also* Chapter 24), and alter respiratory, cardiovascular, gastrointestinal, and neuroendocrine function. δ-Opioid receptor agonists also are potent analgesics in animals, and in isolated cases have proved useful in human beings (Coombs *et al.*, 1985). The main barrier to the clinical use of δ agonists is that most of the available agents are peptides and do not cross the blood–brain barrier, thus requiring intraspinal administration. However, much effort currently is being devoted to the development of clinically useful δ agonists. κ-Selective agonists produce analgesia that has been shown in animals to be mediated primarily at spinal sites. Respiratory depression and miosis may be less severe with κ agonists. Instead of euphoria, κ-receptor agonists produce dysphoric and psychotomimetic effects (Pfeiffer *et al.*, 1986). In neural circuitry mediating both reward and analgesia, μ and κ agonists have been shown to have antagonistic effects (*see* below).

Mixed agonist-antagonist compounds were developed for clinical use with the hope that they would have less addictive potential and less respiratory depression than morphine and related drugs. In practice, however, it has turned out that for the same degree of analgesia, the same intensity of side effects will occur. (American Pain Society, 1999). A "ceiling effect," limiting the amount of analgesia attainable, often is seen with these drugs. Some mixed

agonist-antagonist drugs, such as *pentazocine* and *nalorphine,* can produce severe psychotomimetic effects that are not reversible with naloxone (suggesting that these undesirable side effects are not mediated through classical opioid receptors). Also, pentazocine and nalorphine can precipitate withdrawal in opioid-tolerant patients. For these reasons, the clinical use of these mixed agonist-antagonist drugs is limited.

Analgesia

In human beings, morphine-like drugs produce analgesia, drowsiness, changes in mood, and mental clouding. A significant feature of the analgesia is that it occurs without loss of consciousness. When therapeutic doses of morphine are given to patients with pain, they report that the pain is less intense, less discomforting, or entirely gone; drowsiness commonly occurs. In addition to relief of distress, some patients experience euphoria.

When morphine in the same dose is given to a normal, pain-free individual, the experience may be unpleasant. Nausea is common, and vomiting also may occur. There may be feelings of drowsiness, difficulty in mentation, apathy, and lessened physical activity. As the dose is increased, the subjective, analgesic, and toxic effects, including respiratory depression, become more pronounced. Morphine does not have anticonvulsant activity and usually does not cause slurred speech, emotional lability, or significant motor incoordination.

The relief of pain by morphine-like opioids is relatively selective, in that other sensory modalities are not affected. Patients frequently report that the pain is still present, but that they feel more comfortable (*see* section on Therapeutic Uses of Opioid Analgesics). Continuous, dull pain is relieved more effectively than sharp, intermittent pain, but with sufficient amounts of opioid it is possible to relieve even the severe pain associated with renal or biliary colic.

Any meaningful discussion of the action of analgesic agents must include some distinction between *pain as a specific sensation,* subserved by distinct neurophysiological structures, and *pain as suffering* (the original sensation plus the reactions evoked by the sensation). It is generally agreed that all types of painful experiences, whether produced experimentally or occurring clinically as a result of pathology, include both the original sensation and the reaction to that sensation. It also is important to distinguish between pain caused by stimulation of nociceptive receptors and transmitted over intact neural pathways (*nociceptive* pain) and pain that is caused by damage to neural structures, often involving neural supersensitivity (*neuropathic* pain). Although nociceptive pain usually is responsive to opioid analgesics, neuropathic pain typically responds poorly to opioid analgesics and may require higher doses of drug (McQuay, 1988).

In clinical situations, pain cannot be terminated at will, and the meaning of the sensation and the distress it engenders are markedly affected by the individual's previous experiences and current expectations. In experimentally produced pain, measurements of the effects of morphine on pain threshold have not always been consistent; some workers find that opioids reliably elevate the threshold, while many others do not obtain consistent changes. In contrast, moderate doses of morphine-like analgesics are effective in relieving clinical pain and increasing the capacity to tolerate experimentally induced pain. Not only is the sensation of pain altered by opioid analgesics, but the affective response is changed as well. This latter effect is best assessed by asking patients with clinical pain about the degree of relief produced by the drug administered. When pain does not evoke its usual responses (anxiety, fear, panic, and suffering), a patient's ability to tolerate the pain may be markedly increased even when the capacity to perceive the sensation is relatively unaltered. It is clear, however, that alteration of the emotional reaction to painful stimuli is not the sole mechanism of analgesia. Intrathecal administration of opioids can produce profound segmental analgesia without causing significant alteration of motor or sensory function or subjective effects (Yaksh, 1988).

Mechanisms and Sites of Opioid-Induced Analgesia. While cellular and molecular studies of opioid receptors are invaluable in understanding their function, it is critical to place them in their anatomical and physiological context to fully understand the opioid system. Pain control by opioids needs to be considered in the context of brain circuits modulating analgesia and the functions of the various receptor types in these circuits. Excellent reviews of this topic are available (Fields *et al.,* 1991; Harris, 1996).

It has been well established that the analgesic effects of opioids arise from their ability to inhibit directly the ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, *via* the rostral ventromedial medulla, to the spinal cord dorsal horn. Opioid peptides and their receptors are found throughout these descending pain control circuits (Mansour *et al.,* 1995; Gutstein *et al.,* 1998). μ-Opioid receptor mRNA and/or ligand binding is seen throughout the periaqueductal grey (PAG), pontine retricular formation, median raphe, nucleus raphe magnus, and adjacent gigantocellular reticular nucleus in the rostral ventromedial medulla (RVM) and spinal cord. Evaluation of discrepancies between levels of ligand binding and mRNA expression provides important insights into the mechanisms of μ-opioid receptor-mediated analgesia. For instance, the presence of significant μ-opioid receptor ligand binding in the superficial dorsal horn but scarcity of mRNA expression (Mansour *et al.,* 1995) suggests that the majority of these spinal μ-receptor ligand binding sites are located presynaptically on the terminals of primary afferent nociceptors. This conclusion is consistent with the high levels of μ-opioid receptor mRNA observed in dorsal root ganglia (DRG). A similar mismatch between μ-receptor ligand binding and mRNA expression is seen in the dorsolateral PAG (a high level of binding and sparse mRNA) (Gutstein *et al.,* 1998). δ-Opioid receptor mRNA and ligand binding have been demonstrated in the ventral and ventrolateral quadrants of the PAG, the pontine reticular

formation, and the gigantocellular reticular nucleus, but only low levels are seen in the median raphe and nucleus raphe magnus. As with the μ-opioid receptor, there are significant numbers of δ-opioid receptor binding sites in the dorsal horn but no detectable mRNA expression, suggesting an important role for presynaptic actions of the δ-opioid receptor in spinal analgesia. κ-Opioid receptor mRNA and ligand binding are widespread throughout the PAG, pontine reticular formation, median raphe, nucleus raphe magnus and adjacent gigantocellular reticular nucleus. Again, κ-receptor ligand binding but minimal mRNA have been found in the dorsal horn. Although all three receptor mRNAs are found in the DRG, they are localized on different types of primary afferent cells. μ-Opioid receptor mRNA is present in medium and large diameter DRG cells, δ-opioid receptor mRNA in large diameter cells, and κ-opioid receptor mRNA in small and medium diameter cells (Mansour *et al.*, 1995). This differential localization might be linked to functional differences in pain modulation.

The distribution of opioid receptors in descending pain control circuits indicates substantial overlap between μ and κ receptors. μ Receptors and κ receptors are most anatomically distinct from the δ-opioid receptor in the PAG, median raphe, and nucleus raphe magnus (Gutstein *et al.*, 1998). A similar differentiation of μ and κ receptors from δ is seen in the thalamus, suggesting that interactions between the κ receptor and the μ receptor may be important for modulating nociceptive transmission from higher nociceptive centers as well as in the spinal cord dorsal horn. The actions of μ-receptor agonists are invariably analgesic, whereas those of κ-receptor agonists can be either analgesic or antianalgesic. Consistent with the anatomical overlap between the μ and κ receptors, the antianalgesic actions of the κ-receptor agonists appear to be mediated by functional antagonism of the actions of μ-receptor agonists. The μ receptor produces analgesia within descending pain control circuits, at least in part, by the removal of GABAergic inhibition of RVM-projecting neurons in the PAG and spinally projecting neurons in the RVM (Fields *et al.*, 1991). The pain-modulating effects of the κ-receptor agonists in the brainstem appear to oppose those of μ-receptor agonists. Application of a κ-opioid agonist hyperpolarizes the same RVM neurons that are depolarized by a μ-opioid agonist, and microinjections of a κ-receptor agonist into the RVM antagonize the analgesia produced by microinjections of μ agonists into this region (Pan *et al.*, 1997). This is the strongest evidence to date demonstrating that opioids can have antianalgesic as well as analgesic effects. This finding may explain behavioral evidence for a reduction in hyperalgesia that follows injections of naloxone under certain circumstances.

As mentioned above, there is significant opioid-receptor ligand binding, and little detectable receptor mRNA expression in the spinal cord dorsal horn, but high levels of opioid-receptor mRNA in DRG. This distribution might suggest that the actions of opioid-receptor agonists relevant to analgesia at the spinal level are predominantly presynaptic. At least one presynaptic mechanism with potential clinical significance is inhibition of spinal tachykinin signaling. It is well known that opioids decrease the pain-evoked release of tachykinins from primary afferent nociceptors (Jessell and Iversen, 1977; Yaksh *et al.*, 1980). Recently, the significance of this effect has been questioned. Trafton *et al.* (1999) have demonstrated that at least 80% of tachykinin signaling in response to noxious stimulation remains intact after the intrathecal administration of large doses of opioids. These results suggest that, while opioid administration may reduce tachykinin release from primary afferent nociceptors, this reduction has little functional impact on the actions of tachykinins on postsynaptic pain-transmitting neurons. This implies that either tachykinins are not central to pain signaling and/or opioid-induced analgesia at the spinal level or that, contrary to the conclusions suggested by anatomical studies, presynaptic opioid actions may be of little analgesic significance.

Just as important insights have been made into mechanisms of opioid-induced analgesia at the brainstem and spinal levels, progress also has been made in understanding forebrain mechanisms. It is well known that the actions of opioids in bulbospinal pathways are critical to their analgesic efficacy. The precise role of forebrain actions of opioids and whether or not these actions are independent of those in bulbospinal pathways are less well defined. It is clear that opioid actions in the forebrain contribute to analgesia, because decerebration prevents analgesia when rats are tested for pain sensitivity using the formalin test (Matthies and Franklin, 1992), and microinjection of opioids into several forebrain regions are analgesic in this test (Manning *et al.*, 1994). However, because these manipulations frequently do not change the analgesic efficacy of opioids in measures of acute phasic nociception, such as the tailflick test, a distinction has been made between forebrain-dependent mechanisms for morphine-induced analgesia in the presence of tissue injury and bulbospinal mechanisms for this analgesia in the absence of tissue injury. In an important series of experiments, Manning and Mayer (1995a; 1995b) have shown that this distinction is not absolute. Analgesia induced by systemic administration of morphine in both the tailflick and formalin tests was disrupted either by lesioning or reversibly inactivating the central nucleus of the amygdala, demonstrating that opioid actions in the forebrain contribute to analgesia in measures of tissue damage as well as acute, phasic nociception. The involvement of the amygdala in analgesia is intriguing, as the amygdala has been implicated in the environmental activation of pain control circuits, and it projects extensively to brainstem regions involved in descending pain control (Manning and Mayer, 1995a; 1995b).

Simultaneous administration of morphine at both spinal and supraspinal sites results in synergy in analgesic response, with a tenfold reduction in the total dose of morphine necessary to produce equivalent analgesia at either site alone. The mechanisms responsible for spinal/supraspinal synergy are readily distinguished from those involved with supraspinal analgesia (Pick *et al.*, 1992a). In addition to the well-described spinal/supraspinal synergy, synergistic μ/μ- and μ/δ-agonist interactions also have been observed within the brainstem between the periaqueductal gray, locus coeruleus, and nucleus raphe magnus (Rossi *et al.*, 1993).

Opioids also can produce analgesia when administered peripherally. Opioid receptors are present on peripheral nerves (Fields *et al.*, 1980) and will respond to peripherally applied opioids and locally released endogenous opioid compounds when "up-regulated" during inflammatory pain states (Stein *et al.*, 1991; Stein, 1993). During inflammation, immune cells capable of releasing endogenous opioids are present near sensory nerves, and a perineural defect allows opioids access to the nerves (Stein, 1993; Stein, 1995). It appears that this also may occur in neuropathic pain models (Kayser *et al.*, 1995), perhaps because of the presence of immune cells near damaged nerves (Monaco *et al.*, 1992) and perineural defects extant in these conditions.

The Role of N/OFQ and Its Receptor in Pain Modulation. N/OFQ mRNA and peptide are present throughout descending pain control circuits. For instance, N/OFQ-containing neurons are present in the PAG, the median raphe, throughout the RVM, and in the superficial dorsal horn (Neal *et al.*, 1999b). This distribution overlaps with that of opioid peptides, but the extent of colocalization remains unclear. N/OFQ-receptor ligand binding and mRNA are seen in the PAG, median raphe, and RVM (Neal *et al.*, 1999a). Spinally, there is stronger N/OFQ-receptor mRNA expression in the ventral horn than in the dorsal horn, but higher levels of ligand binding in the dorsal horn. There also are high N/OFQ-receptor mRNA levels in the DRG.

Despite clear anatomical evidence for a role of the N/OFQ system in pain modulation, its function remains unclear. Targeted disruption of the N/OFQ receptor in mice had little effect on basal pain sensitivity in several measures, whereas targeted disruption of the N/OFQ precursor consistently elevated basal responses in the tailflick test, suggesting an important role for N/OFQ in regulating basal pain sensitivity (Nishi *et al.*, 1997; Koster *et al.*, 1999). Intrathecal injections of N/OFQ have been shown to be analgesic (Yamamoto *et al.*, 1997; Xu *et al.*, 1996); however, supraspinal administration has produced either hyperalgesia, antiopioid effects, or a biphasic hyperalgesic/analgesic response (Rossi *et al.*, 1996b, Rossi *et al.*, 1997; Grisel *et al.*, 1996). These conflicting findings may be explained in part by a study in which it was shown that N/OFQ inhibits both pain-facilitating and analgesia-facilitating neurons in the RVM (Pan *et al.*, 2000). Activation of endogenous analgesic circuitry was blocked by administration of N/OFQ. If the animal was hyperalgesic, the enhanced pain sensitivity also was blocked by N/OFQ. Thus, the effects of N/OFQ on pain responses appear to depend on the preexisting state of pain in the animal.

Mood Alterations and Rewarding Properties

The mechanisms by which opioids produce euphoria, tranquility, and other alterations of mood (including rewarding properties) are not entirely clear. However, the neural systems that mediate opioid reinforcement are distinct from those involved in physical dependence and analgesia (Koob and Bloom, 1988). Behavioral and pharmacological evidence points to the role of dopaminergic pathways, particularly involving the nucleus accumbens (NAcc), in drug-induced reward. There is ample evidence for interactions between opioids and dopamine in mediating opioid-induced reward.

A full appreciation of mechanisms of drug-induced reward requires a more complete understanding of the NAcc and related structures at the anatomical level as well as a careful examination of the interface between the opioid system and dopamine receptors. The NAcc, portions of the olfactory tubercle, and the ventral and medial portions of the caudate-putamen constitute an area referred to as the ventral striatum (Heimer *et al.*, 1982). The ventral striatum is implicated in motivation and affect (limbic functions), while the dorsal striatum is involved in sensorimotor and cognitive functions (Willner *et al.*, 1991). Both the dorsal and ventral striatum are heterogeneous structures that can be subdivided into distinct compartments. In the middle and caudal third of the NAcc, the characteristic distribution of neuroactive substances results in two unique compartments termed the core and the shell (Zahm and Heimer, 1988; Heimer *et al.*, 1991). It is important to note that other reward-relevant brain regions (*e.g.*, the lateral hypothalamus and medial prefrontal cortex) implicated with a variety of abused drugs are connected reciprocally to the shell of the NAcc. Thus, the *shell of the NAcc* is the site that may be involved directly in the emotional and motivational aspects of drug-induced reward.

Prodynorphin- and proenkephalin-derived opioid peptides are expressed primarily in *output neurons* of the striatum and NAcc. All three opioid receptor types are present in the NAcc (Mansour *et al.*, 1988) and are thought to mediate, at least in part, the motivational effects of opiate drugs. Selective μ- and δ-receptor agonists are rewarding when defined by place preference (Shippenberg *et al.*, 1992) and intracranial self-administration (Devine and Wise, 1994) paradigms. Conversely, selective κ-receptor agonists produce aversive effects (Cooper, 1991; Shippenberg *et al.*, 1992). Naloxone and selective μ antagonists also produce aversive effects (Cooper, 1991). Positive motivational effects of opioids are partially mediated by dopamine release at the level of the NAcc. Thus, κ-receptor activation in these circuits inhibits dopamine release (Mulder *et al.*, 1991; Mulder and Schoffelmeer, 1993), while μ- and δ-receptor activation increases dopamine release (Chesselet *et al.*, 1983; Devine *et al.*, 1993). Distinctive cell clusters in the shell of the accumbens contain proenkephalin, prodynorphin, μ receptors, and κ receptors as well as dopamine receptors. These clusters possibly could be a region where the motivational properties of dopaminergic and opioid drugs are processed. The potential role of these structures and the neural circuits in which they are embedded in the rewarding effects of opioids will be of great interest.

The locus ceruleus (LC) contains both noradrenergic neurons and high concentrations of opioid receptors and is postulated to play a critical role in feelings of alarm, panic, fear, and anxiety. Neural activity in the LC is inhibited by both exogenous opioids and endogenous opioid-like peptides.

Other CNS Effects

While opioids are used clinically primarily for their pain-relieving properties, they produce a host of other effects. This is not surprising in view of the wide distribution of opioids and their receptors, both in the brain and in the periphery. A brief summary of some of these effects is presented below. High doses of opioids can produce muscular rigidity in human beings. Chest wall rigidity severe enough to compromise respiration is not uncommon during anesthesia with fentanyl, alfentanil, remifentanil, and sufentanil (*see* Monk *et al.*, 1988). Opioids and endogenous peptides cause catalepsy, circling, and stereotypical behavior in rats and other animals.

Effects on the Hypothalamus. Opioids alter the equilibrium point of the hypothalamic heat-regulatory mechanisms, such that

body temperature usually falls slightly. However, chronic high dosage may increase body temperature (*see* Martin, 1983).

Neuroendocrine Effects. Morphine acts in the hypothalamus to inhibit the release of gonadotropin-releasing hormone (GnRH) and corticotropin-releasing factor (CRF), thus decreasing circulating concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), ACTH, and β-endorphin; the last two peptides usually are released simultaneously from corticotropes in the pituitary. As a result of the decreased concentrations of pituitary trophic hormones, the concentrations of testosterone and cortisol in plasma decline. Secretion of thyrotropin is relatively unaffected.

The administration of μ agonists increases the concentration of prolactin in plasma, probably by reducing the dopaminergic inhibition of its secretion. Although some opioids enhance the secretion of growth hormone, the administration of morphine or β-endorphin has little effect on the concentration of the hormone in plasma. With chronic administration, tolerance develops to the effects of morphine on hypothalamic releasing factors. Observations in patients maintained on methadone reflect this phenomenon; in women, menstrual cycles that had been disrupted by intermittent use of heroin return to normal; in men, circulating concentrations of LH and testosterone are usually within the normal range.

Although κ-receptor agonists inhibit the release of antidiuretic hormone and cause diuresis, the administration of μ-opioid agonists tends to produce antidiuretic effects in human beings. The effects of opioids on neuroendocrine function have been reviewed by (Howlett and Rees, 1986) and by (Grossman, 1988).

Miosis. Morphine and most μ and κ agonists cause constriction of the pupil by an excitatory action on the parasympathetic nerve innervating the pupil. Following toxic doses of μ agonists, *the miosis is marked and pinpoint pupils are pathognomonic;* however, marked mydriasis occurs when asphyxia intervenes. Some tolerance to the miotic effect develops, but addicts with high circulating concentrations of opioids continue to have constricted pupils. Therapeutic doses of morphine increase accommodative power and lower intraocular tension in both normal and glaucomatous eyes.

Convulsions. In animals, high doses of morphine and related opioids produce convulsions. Several mechanisms appear to be involved, and different types of opioids produce seizures with different characteristics. Morphine-like drugs excite certain groups of neurons, especially hippocampal pyramidal cells; these excitatory effects probably result from inhibition of the release of GABA by interneurons (*see* McGinty and Friedman, 1988). Selective δ agonists produce similar effects. These actions may contribute to the seizures that are produced by some agents at doses only moderately higher than those required for analgesia, especially in children. However, with most opioids, convulsions occur only at doses far in excess of those required to produce profound analgesia, and seizures are not seen when potent μ agonists are used to produce anesthesia. Naloxone is more potent in antagonizing convulsions produced by some opioids (*e.g.*, morphine, methadone, and propoxyphene) than those produced by others (*e.g.*, meperidine). The production of convulsant metabolites of the latter agent may be partially responsible (*see* below). Anticonvulsant agents may not always be effective in suppressing opioid-induced seizures.

Respiration. Morphine-like opioids depress respiration, at least in part by virtue of a direct effect on the brainstem respiratory centers. The respiratory depression is discernible even with doses too small to disturb consciousness and increases progressively as the dose is increased. In human beings, death from morphine poisoning is nearly always due to respiratory arrest. Therapeutic doses of morphine in human beings depress all phases of respiratory activity (rate, minute volume, and tidal exchange) and also may produce irregular and periodic breathing. The diminished respiratory volume is due primarily to a slower rate of breathing, and with toxic amounts the rate may fall to 3 or 4 breaths per minute. Although effects on respiration are readily demonstrated, clinically significant respiratory depression rarely occurs with standard morphine doses in the absence of underlying pulmonary dysfunction. However, the combination of opioids with other medications, such as general anesthetics, tranquilizers, alcohol, or sedative-hypnotics, may present a greater risk of respiratory depression. Maximal respiratory depression occurs within 5 to 10 minutes after intravenous administration of morphine or within 30 or 90 minutes following intramuscular or subcutaneous administration, respectively.

Maximal respiratory depressant effects occur more rapidly with more lipid-soluble agents. Following therapeutic doses, respiratory minute volume may be reduced for as long as 4 to 5 hours. The primary mechanism of respiratory depression by opioids involves a reduction in the responsiveness of the brainstem respiratory centers to carbon dioxide. Opioids also depress the pontine and medullary centers involved in regulating respiratory rhythmicity and the responsiveness of medullary respiratory centers to electrical stimulation (*see* Martin, 1983).

Hypoxic stimulation of the chemoreceptors still may be effective when opioids have decreased the responsiveness to CO_2, and the inhalation of O_2 may thus produce apnea. After large doses of morphine or other μ agonists, patients will breathe if instructed to do so, but without such instruction they may remain relatively apneic.

Because of the accumulation of CO_2, respiratory rate and sometimes even minute volume can be unreliable indicators of the degree of respiratory depression that has been produced by morphine. Natural sleep also produces a decrease in the sensitivity of the medullary center to CO_2, and the effects of morphine and sleep are additive.

Numerous studies have compared morphine and morphine-like opioids with respect to their ratios of analgesic to respiratory-depressant activities. Most studies have found that, when equianalgesic doses are used, the degree of respiratory depression observed with morphine-like opioids is not significantly different from that seen with morphine. Severe respiratory depression is less likely after the administration of large doses of selective κ agonists. High concentrations of opioid receptors and of endogenous peptides are found in the medullary areas believed to be important in ventilatory control.

Cough. Morphine and related opioids also depress the cough reflex, at least in part by a direct effect on a cough center in the medulla. There is, however, no obligatory relationship between depression of respiration and depression of coughing, and effective antitussive agents are available that do not depress respiration (*see* below). Suppression of cough by such agents appears to involve receptors in the medulla that are less sensitive to naloxone than are those responsible for analgesia.

Nauseant and Emetic Effects. Nausea and vomiting produced by morphine-like drugs are unpleasant side effects caused by direct stimulation of the chemoreceptor trigger zone for emesis, in the area postrema of the medulla. Certain individuals never vomit after morphine, whereas others do so each time the drug is administered.

Nausea and vomiting are relatively uncommon in recumbent patients given therapeutic doses of morphine, but nausea occurs in approximately 40% and vomiting in 15% of ambulatory patients given 15 mg of the drug subcutaneously. This suggests that a vestibular component also is operative. Indeed, the nauseant and emetic effects of morphine are markedly enhanced by vestibular stimulation, and morphine and related synthetic analgesics produce an increase in vestibular sensitivity. All clinically useful μ agonists produce some degree of nausea and vomiting. Careful, controlled clinical studies usually demonstrate that, in equianalgesic dosage, the incidence of such side effects is not significantly lower than that seen with morphine. Drugs that are useful in motion sickness are sometimes helpful in reducing opioid-induced nausea in ambulatory patients; phenothiazines are also useful (*see* Chapter 20).

Cardiovascular System

In the supine patient, therapeutic doses of morphine-like opioids have no major effect on blood pressure or cardiac rate and rhythm. Such doses do produce peripheral vasodilation, reduced peripheral resistance, and an inhibition of baroreceptor reflexes. Therefore, when supine patients assume the head-up position, orthostatic hypotension and fainting may occur. The peripheral arteriolar and venous dilation produced by morphine involves several mechanisms. Morphine and some other opioids provoke release of histamine, which sometimes plays a large role in the hypotension. However, vasodilation is usually only partially blocked by H_1 antagonists, but it is effectively reversed by naloxone. Morphine also blunts the reflex vasoconstriction caused by increased P_{CO_2}.

Effects on the myocardium are not significant in normal individuals. In patients with coronary artery disease but no acute medical problems, 8 to 15 mg of morphine administered intravenously produces a decrease in oxygen consumption, left ventricular end-diastolic pressure, and cardiac work; effects on cardiac index are usually slight (Sethna *et al.*, 1982). In patients with acute myocardial infarction, the cardiovascular responses to morphine may be more variable than in normal subjects, and the magnitude of changes (*e.g.*, the decrease in blood pressure) may be more pronounced (*see* Roth *et al.*, 1988).

Morphine may exert its well-known therapeutic effect in the treatment of angina pectoris and acute myocardial infarction by decreasing preload, inotropy, and chronotropy, thus favorably altering determinants of myocardial oxygen consumption and helping to relieve ischemia. It is not clear whether the analgesic properties of morphine in this situation are due to the reversal of acidosis that may stimulate local acid-sensing ion channels (Benson *et al.*, 1999; McCleskey and Gold, 1999) or to a direct analgesic effect on nociceptive afferents from the heart.

When administered prior to experimental ischemia, morphine has been shown to produce cardioprotective effects. Morphine can mimic the phenomenon of ischemic preconditioning, where a short ischemic episode paradoxically protects the heart against further ischemia. This effect appears to be mediated through δ receptors signaling through a mitochondrial ATP-sensitive potassium channel in cardiac myocytes; the effect also is produced by other G protein-coupled receptors signaling through G_i subunits (Fryer *et al.*, 2000; Liang and Gross, 1999; Schultz *et al.*, 1996). It also has been suggested recently that δ opioids can be antiarrhythmic and antifibrillatory during and after periods of ischemia (Fryer *et al.*, 2000). Other data, however, suggest that δ opioids can be arrythmogenic (McIntosh *et al.*, 1992).

Very large doses of morphine can be used to produce anesthesia; however, decreased peripheral resistance and blood pressure are troublesome. Fentanyl and sufentanil, which are potent and selective μ agonists, are less likely to cause hemodynamic instability during surgery, in part because they do not cause the release of histamine (Monk *et al.*, 1988).

Morphine-like opioids should be used with caution in patients who have a decreased blood volume, since these agents can aggravate hypovolemic shock. Morphine should be used with great care in patients with cor pulmonale, since deaths following ordinary therapeutic doses have been reported. The concurrent use of certain phenothiazines may increase the risk of morphine-induced hypotension.

Cerebral circulation is not directly affected by therapeutic doses of morphine. However, opioid-induced respiratory

depression and CO_2 retention can result in cerebral vasodilation and an increase in cerebrospinal fluid pressure; the pressure increase does not occur when P_{CO_2} is maintained at normal levels by artificial ventilation.

Gastrointestinal Tract

Stomach. Morphine and other μ agonists usually decrease the secretion of hydrochloric acid, although stimulation is sometimes evident. Activation of opioid receptors on parietal cells enhances secretion, but indirect effects, including increased secretion of somatostatin from the pancreas and reduced release of acetylcholine, appear to be dominant in most circumstances (*see* Kromer, 1988). Relatively low doses of morphine decrease gastric motility, thereby prolonging gastric emptying time; this can increase the likelihood of esophageal reflux (*see* Duthie and Nimmo, 1987). The tone of the antral portion of the stomach and of the first part of the duodenum is increased, which often makes therapeutic intubation of the duodenum more difficult. Passage of the gastric contents through the duodenum may be delayed by as much as 12 hours, and the absorption of orally administered drugs is retarded.

Small Intestine. Morphine diminishes biliary, pancreatic, and intestinal secretions (Dooley *et al.*, 1988) and delays digestion of food in the small intestine. Resting tone is increased, and periodic spasms are observed. The amplitude of the nonpropulsive type of rhythmic, segmental contractions usually is enhanced, but propulsive contractions are markedly decreased. The upper part of the small intestine, particularly the duodenum, is affected more than the ileum. A period of relative atony may follow the hypertonicity. Water is absorbed more completely because of the delayed passage of bowel contents, and intestinal secretion is decreased; this increases the viscosity of the bowel contents.

In the presence of intestinal hypersecretion that may be associated with diarrhea, morphine-like drugs inhibit the transfer of fluid and electrolytes into the lumen by naloxone-sensitive actions on the intestinal mucosa and within the CNS. Enterocytes may possess opioid receptors, but this hypothesis is controversial. However, it is clear that opioids exert important effects on the submucosal plexus that lead to a decrease in the basal secretion by enterocytes and inhibition of the stimulatory effects of acetylcholine, prostaglandin E_2, and vasoactive intestinal peptide. The effects of opioids initiated either in the CNS or the submucosal plexus may be mediated in large part by the release of norepinephrine and stimulation of α_2-adrenergic receptors on enterocytes (*see* Coupar, 1987). The actions of opioids on intestinal secretion have been reviewed by Manara and Bianchetti (1985) and Kromer (1988).

Large Intestine. Propulsive peristaltic waves in the colon are diminished or abolished after administration of morphine, and tone is increased to the point of spasm. The resulting delay in the passage of bowel contents causes considerable desiccation of the feces, which, in turn, retards their advance through the colon. The amplitude of the nonpropulsive type of rhythmic contractions of the colon usually is enhanced. The tone of the anal sphincter is greatly augmented, and reflex relaxation in response to rectal distension is reduced. These actions, combined with inattention to the normal sensory stimuli for defecation reflex due to the central actions of the drug, contribute to morphine-induced constipation.

Mechanism of Action on the Bowel. The usual gastrointestinal effects of morphine primarily are mediated by μ- and δ-opioid receptors in the bowel. However, injection of opioids into the cerebral ventricles or in the vicinity of the spinal cord can inhibit gastrointestinal propulsive activity as long as the extrinsic innervation to the bowel is intact. The relatively poor penetration of morphine into the CNS may explain how preparations such as paregoric can produce constipation at less than analgesic doses and may account for troublesome gastrointestinal side effects during the use of oral morphine for the treatment of cancer pain (*see* Manara and Bianchetti, 1985). Although some tolerance develops to the effects of opioids on gastrointestinal motility, patients who take opioids chronically remain constipated.

Biliary Tract. After the subcutaneous injection of 10 mg of morphine sulfate, the sphincter of Oddi constricts and the pressure in the common bile duct may rise more than tenfold within 15 minutes; this effect may persist for 2 hours or more. Fluid pressure also may increase in the gallbladder and produce symptoms that may vary from epigastric distress to typical biliary colic.

Some patients with biliary colic may experience exacerbation rather than relief of pain when given these drugs. Spasm of the sphincter of Oddi is probably responsible for elevations of plasma amylase and lipase that are sometimes found after patients are given morphine. Atropine only partially prevents morphine-induced biliary spasm, but opioid antagonists prevent or relieve it. Nitroglycerin (0.6 to 1.2 mg) administered sublingually also decreases the elevated intrabiliary pressure (*see* Staritz, 1988).

Other Smooth Muscle

Ureter and Urinary Bladder. Therapeutic doses of morphine may increase the tone and amplitude of contractions of the ureter, although the response is variable. When the antidiuretic effects of the drug are prominent and urine flow decreases, the ureter may become quiescent.

Morphine inhibits the urinary voiding reflex, and both the tone of the external sphincter and the volume of the bladder are increased; catheterization is sometimes required following therapeutic doses of morphine. Stimulation of either μ or δ

receptors in the brain or in the spinal cord exerts similar actions on bladder motility (*see* Dray and Nunan, 1987). Tolerance develops to these effects of opioids on the bladder.

Uterus. If the uterus has been made hyperactive by oxytocics, morphine tends to restore tone, frequency, and the amplitude of contractions to normal. Parenteral administration of opioids within 2 to 4 hours of delivery may lead to transient respiratory depression in the neonate due to transplacental passage of opioids. This may be treated readily with naloxone.

Skin

Therapeutic doses of morphine cause dilation of cutaneous blood vessels. The skin of the face, neck, and upper thorax frequently becomes flushed. These changes may be due in part to the release of histamine and may be responsible for the sweating and some of the pruritus that occasionally follow the systemic administration of morphine (*see* below). Histamine release probably accounts for the urticaria commonly seen at the site of injection; this is not mediated by opioid receptors and is not blocked by naloxone. It is seen with morphine and meperidine, but not with oxymorphone, methadone, fentanyl, or sufentanil (*see* Duthie and Nimmo, 1987).

Pruritus is a common and potentially disabling complication of opioid use. It can be caused by intraspinal and systemic injections of opioids, but it appears to be more intense after intraspinal administration (Ballantyne *et al.*, 1988). The effect appears to be mediated in large part by dorsal horn neurons and is reversible by naloxone (Thomas *et al.*, 1992). An intriguing report suggested that systemic morphine could partially inhibit pruritus caused by intraspinal administration of morphine, implying the existence of an opioid-mediated, itch-inhibition system, possibly supraspinal in origin (Thomas *et al.*, 1993).

Immune System

The effects of opioids on the immune system are complex. Opioids have been shown to modulate immune function by direct effects on cells of the immune system and indirectly *via* centrally mediated neuronal mechanisms (Sharp and Yaksh, 1997). It appears that acute, central immunomodulatory effects of opioids may be mediated by activation of the sympathetic nervous system, whereas the chronic effects of opioids may involve modulation of hypothalamic-pituitary-adrenal (HPA) axis function (Mellon and Bayer, 1998). Direct effects on immune cells may involve unique and as yet incompletely characterized variants of the classical neuronal opioid receptors, with δ-receptor variants being more prominent (Sharp and Yaksh, 1997). Atypical receptors could account for the fact that it has been very difficult to demonstrate significant opioid binding on immune cells in spite of the observance of robust functional effects. In contrast, morphine-induced immune suppression is largely abolished in mice lacking the μ-receptor gene, suggesting that the μ receptor is a major target of morphine's actions on the immune system (Gaveriaux-Ruff *et al.*, 1998). A potential mechanism for the immune suppressive effects of morphine on neutrophils was proposed recently by Welters *et al.* (2000), who demonstrated that NF-κB activation induced by an inflammatory stimulus was inhibited by morphine in a nitric oxide-dependent manner. Another group of investigators has proposed that the induction and activation of MAP kinase also may play a role (Chuang *et al.*, 1997).

The overall effects of opioids on immune function appear to be suppressive; increased susceptibility to infection and tumor spread have been observed in experimental settings. Infusion of the μ-receptor antagonist naloxone has been shown to improve survival after experimentally induced sepsis (Risdahl *et al.*, 1998). Such effects have been inconsistent in clinical situations, possibly because of the use of confounding therapies and necessary opioid analgesics. In some situations, effects on immune function appear more prominent with acute administration than with chronic administration, which could have important implications for the care of the critically ill (Sharp and Yaksh, 1997). In contrast, opioids have been shown to reverse pain-induced immunosuppression and increased tumor metastatic potential in animal models (Page and Ben-Eliyahu, 1997). Therefore, opioids may either inhibit or augment immune function depending on the context in which they are used. These studies also indicate that withholding opioids in the presence of pain in immunocompromised patients could actually worsen immune function. An intriguing recent paper indicated that the partial μ-receptor agonist buprenorphine (*see* below) did not alter immune function when injected centrally into the mesencephalic periaqueductal gray matter, while morphine did (Gomez-Flores and Weber, 2000). Taken together, these studies indicate that opioid-induced immune suppression may be clinically relevant to both the treatment of severe pain and in the susceptibility of opioid addicts to infection (*e.g.*, HIV, tuberculosis). Different opioid agonists also may have unique immunomodulatory properties. Better understanding of these properties eventually should help guide rational use of opioids in patients with cancer or at risk for infection or immune compromise.

Tolerance and Physical Dependence

The development of tolerance and physical dependence with repeated use is a characteristic feature of all the opioid drugs. *Tolerance* to the effect of opioids or other drugs simply means that, over time, the drug loses its effectiveness and an increased dose is required to produce the same physiological response. *Dependence* refers to a complex and poorly understood set of changes in the homeostasis of an organism that cause a disturbance of the homeostatic set point of the organism if the drug is stopped. This disturbance often is revealed when administration of an opioid is abruptly stopped, resulting in *withdrawal. Addiction* is a behavioral pattern characterized by compulsive use of a drug and overwhelming involvement with its procurement and use. Tolerance and dependence are physiological responses seen in all patients and are not predictors of addiction (*see* Chapter 24). These processes appear to be quite distinct. For example, cancer pain often requires prolonged treatment with high doses of opioids, leading to tolerance and dependence. Yet, abuse in this setting is very unusual (Foley, 1993). Neither the presence of tolerance and dependence nor the fear that they may develop should *ever* interfere with the appropriate use of opioids. Opioids can be discontinued in dependent patients once the need for analgesics is gone without subjecting them

to withdrawal (*see* Chapter 24). Clinically, the dose can be decreased by 10% to 20% every other day and eventually stopped without signs and symptoms of withdrawal.

In vivo studies in animal models demonstrate the importance of other neurotransmitters and their interactions with opioid pathways in the development of tolerance to morphine. Blockade of glutamate actions by NMDA (*N*-methyl-D-aspartate)-receptor antagonists blocks morphine tolerance (Trujillo and Akil, 1997). Since NMDA antagonists have no effect on the potency of morphine in naive animals, their effect cannot be attributed to potentiation of opioid actions. Interestingly, the clinically used antitussive dextromethorphan (*see* below) has been shown to function as an NMDA antagonist. In animals, it can attenuate opioid tolerance development and reverse established tolerance (Elliott *et al.*, 1994). Nitric oxide production, possibly induced by NMDA-receptor activation, also has been implicated in tolerance, as inhibition of nitric oxide synthase (NOS) also blocks morphine tolerance development (Kolesnikov *et al.*, 1993). Administering NOS inhibitors to morphine-tolerant animals also may reverse tolerance in certain circumstances. Although the NMDA antagonists and nitric oxide synthase inhibitors are effective against tolerance to morphine and δ agonists such as DPDPE, they have little effect against tolerance to the κ agonists. Dependence seems to be closely related to tolerance, since the same treatments that block tolerance to morphine also block dependence. Other related signaling systems also are being investigated as mediators of opioid tolerance and dependence. The selective actions of drugs on tolerance and dependence demonstrate that specific mechanisms can be targeted to minimize these two unwanted actions.

MORPHINE AND RELATED OPIOID AGONISTS

There are now many compounds with pharmacological properties similar to those of morphine, yet morphine remains the standard against which new analgesics are measured. However, responses of an individual patient may vary dramatically with different μ-opioid receptor agonists. For example, some patients unable to tolerate morphine may have no problems with an equianalgesic dose of methadone, whereas others can take morphine and not methadone. If problems are encountered with one drug, another should be tried. Mechanisms underlying variations in individual responses to morphine-like agonists are not yet well understood.

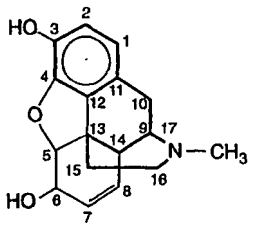
Source and Composition of Opium. Because the laboratory synthesis of morphine is difficult, the drug is still obtained from opium or extracted from poppy straw. Opium is obtained from the unripe seed capsules of the poppy plant, *Papaver somniferum*. The milky juice is dried and powdered to make powdered opium, which contains a number of alkaloids. Only a few—morphine, codeine, and papaverine—have clinical usefulness. These alkaloids can be divided into two distinct chemical classes, *phenanthrenes* and *benzylisoquinolines*. The principal phenanthrenes are *morphine* (10% of opium), *codeine* (0.5%), and *thebaine* (0.2%). The principal benzylisoquinolines are *papaverine* (1.0%), which is a smooth muscle relaxant (*see* the seventh and earlier editions of this book), and *noscapine* (6.0%).

Chemistry of Morphine and Related Opioids. The structure of morphine is shown in Table 23–5. Many semisynthetic derivatives are made by relatively simple modifications of morphine or thebaine. Codeine is methylmorphine, the methyl substitution being on the phenolic hydroxyl group. Thebaine differs from morphine only in that both hydroxyl groups are methylated and that the ring has two double bonds ($\Delta^{6,7}$, $\Delta^{8,14}$). Thebaine has little analgesic action but is a precursor of several important 14-OH compounds, such as oxycodone and naloxone. Certain derivatives of thebaine are more than 1000 times as potent as morphine (*e.g.*, etorphine). Diacetylmorphine, or heroin, is made from morphine by acetylation at the 3 and 6 positions. Apomorphine, which also can be prepared from morphine, is a potent emetic and dopaminergic agonist. Hydromorphone, oxymorphone, hydrocodone, and oxycodone also are made by modifying the morphine molecule. The structural relationships between morphine and some of its surrogates and antagonists are shown in Table 23–5.

Structure-Activity Relationship of the Morphine-Like Opioids. In addition to morphine, codeine, and the semisynthetic derivatives of the natural opium alkaloids, a number of other structurally distinct chemical classes of drugs have pharmacological actions similar to those of morphine. Clinically useful compounds include the morphinans, benzomorphans, methadones, phenylpiperidines, and propionanilides. Although the two-dimensional representations of these chemically diverse compounds appear to be quite different, molecular models show certain common characteristics; these are indicated by the heavy lines in the structure of morphine shown in Table 23–5. Among the important properties of the opioids that can be altered by structural modification are their affinities for various species of opioid receptors, their activities as agonists *versus* antagonists, their lipid solubilities, and their resistance to metabolic breakdown. For example, blockade of the phenolic hydroxyl at position 3, as in codeine and heroin, drastically reduces binding to μ receptors; these compounds are converted to the potent analgesics morphine and 6-acetyl morphine, respectively, *in vivo*.

Absorption, Distribution, Fate, and Excretion. ***Absorption.*** In general, the opioids are readily absorbed from the gastrointestinal tract; absorption through the rectal mucosa is adequate, and a few agents (*e.g.*, morphine, hydromorphone) are available in suppositories. The more lipophilic opioids also are readily absorbed through the nasal or buccal mucosa (Weinberg *et al.*, 1988). Those with the greatest lipid solubility also can be absorbed transdermally (Portenoy *et al.*, 1993). Opioids are absorbed

Table 23–5
Structures of Opioids and Opioid Antagonists Chemically Related to Morphine



MORPHINE

NONPROPRIETARY NAME	CHEMICAL RADICALS AND POSITION*			OTHER CHANGES†
	3	*6*	*17*	
Morphine	—OH	—OH	—CH_3	—
Heroin	—$OCOCH_3$	—$OCOCH_3$	—CH_3	—
Hydromorphone	—OH	=O	—CH_3	(1)
Oxymorphone	—OH	=O	—CH_3	(1), (2)
Levorphanol	—OH	—H	—CH_3	(1), (3)
Levallorphan	—OH	—H	—$CH_2CH{=}CH_2$	(1), (3)
Codeine	—OCH_3	—OH	—CH_3	—
Hydrocodone	—OCH_3	=O	—CH_3	(1)
Oxycodone	—OCH_3	=O	—CH_3	(1), (2)
Nalmefene	—OH	=CH_2	—CH_2— 	(1), (2)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	(1), (2)
Naltrexone	—OH	=O	—CH_2— 	(1), (2)
Buprenorphine	—OH	—OCH_3	—CH_2— 	(1), (4)
Butorphanol	—OH	—H	—CH_2— 	(1), (2), (3)
Nalbuphine	—OH	—OH	—CH_2— 	(1), (2)

*The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown above.
†Other changes in the morphine molecule are as follows:
(1) Single instead of double bond between C7 and C8.
(2) OH added to C14.
(3) No oxygen between C4 and C5.
(4) *Endo*etheno bridge between C6 and C14; 1-hydroxy-1,2,2-trimethylpropyl substitution on C7.

readily after subcutaneous or intramuscular injection and can adequately penetrate the spinal cord following epidural or intrathecal administration (*also see* section on alternative routes of administration). Small amounts of morphine introduced epidurally or intrathecally into the spinal canal can produce profound analgesia that may last 12 to 24 hours. However, due to the hydrophilic nature of morphine, there is rostral spread of the drug in spinal fluid, and side effects, especially respiratory depression, can emerge up to 24 hours later as the opioid reaches supraspinal respiratory control centers. With highly lipophilic agents such as hydromorphone or fentanyl, rapid absorption by spinal neural tissues produces very localized effects and segmental analgesia. The duration of action

is shorter because of distribution of the drug in the systemic circulation, and the severity of respiratory depression may be more directly proportional to its concentration in plasma, due to a lesser degree of rostral spread (Gustafsson and Wiesenfeld-Hallin, 1988). However, patients receiving epidural or intrathecal fentanyl still should be monitored for respiratory depression.

With most opioids, including morphine, the effect of a given dose is less after oral than after parenteral administration, due to variable but significant first-pass metabolism in the liver. For example, the bioavailability of oral preparations of morphine is only about 25%. The shape of the time-effect curve also varies with the route of administration, so that the duration of action is often somewhat longer with the oral route. If adjustment is made for variability of first-pass metabolism and clearance, it is possible to achieve adequate relief of pain by the oral administration of morphine. Satisfactory analgesia in cancer patients has been associated with a very broad range of steady-state concentrations of morphine in plasma (16 to 364 ng/ml; Neumann *et al.,* 1982).

When morphine and most opioids are given intravenously, they act promptly. However, the more lipid-soluble compounds act more rapidly than morphine after subcutaneous administration because of differences in the rates of absorption and entry into the CNS. Compared with other more lipid-soluble opioids such as codeine, heroin, and methadone, morphine crosses the blood–brain barrier at a considerably lower rate.

Distribution and Fate. When therapeutic concentrations of morphine are present in plasma, about one-third of the drug is protein bound. Morphine itself does not persist in tissues, and 24 hours after the last dose tissue concentrations are low.

The major pathway for the metabolism of morphine is conjugation with glucuronic acid. The two major metabolites formed are *morphine-6-glucuronide* and *morphine-3-glucuronide.* Small amounts of morphine 3,6, diglucuronide also may be formed. Although the 3- and 6-glucuronides are quite polar, both can cross the blood–brain barrier to exert significant clinical effects (Christup, 1997). Morphine-6-glucuronide has pharmacological actions indistinguishable from those of morphine. Morphine-6-glucuronide given systemically is approximately twice as potent as morphine in animal models (Paul *et al.,* 1989) and in human beings (Osborne *et al.,* 1988). With chronic administration, it accounts for a significant portion of morphine's analgesic actions (Osborne *et al.,* 1988; Osborne *et al.,* 1990; Portenoy *et al.,* 1991; Portenoy *et al.,* 1992). Indeed, with chronic oral dosing, the blood levels of morphine-6-glucuronide typically exceed those of morphine. Given its greater potency as well as its higher concentrations, morphine-6-glucuronide may be responsible for most of morphine's analgesic activity in patients receiving chronic oral morphine. Morphine-6-glucuronide is excreted by the kidney. In renal failure, the levels of morphine-6-glucuronide can accumulate, perhaps explaining morphine's potency and long duration in patients with compromised renal function. In young adults, the half-life of morphine is about 2 hours; the half-life of morphine-6-glucuronide is somewhat longer. Children achieve adult renal function values by 6 months of age. In elderly patients, lower morphine doses are recommended, based on its smaller volume of distribution (Owen *et al.,* 1983) and the general decline in renal function in the elderly. The 3-glucuronide, also an important metabolite of morphine (Milne *et al.,* 1996), has little affinity for opioid receptors but may contribute to excitatory effects of morphine (Smith, 2000). Some investigators also have shown that morphine-3-glucuronide can antagonize morphine-induced analgesia (Smith *et al.,* 1990), but this finding is not universal (Christup, 1997). Morphine also is metabolized by other pathways. *N*-demethylation to normorphine is a minor metabolic pathway in human beings but is more prominent in rodents (Yeh *et al.,* 1977). *N*-dealkylation is important in the metabolism of some congeners of morphine.

Excretion. Very little morphine is excreted unchanged. It is eliminated by glomerular filtration, primarily as morphine-3-glucuronide; 90% of the total excretion takes place during the first day. Enterohepatic circulation of morphine and its glucuronides occurs, which accounts for the presence of small amounts of morphine in the feces and in the urine for several days after the last dose.

Codeine. In contrast to morphine, codeine is approximately 60% as effective orally as parenterally, both as an analgesic and as a respiratory depressant. Codeine, like levorphanol, oxycodone, and methadone, has a high oral to parenteral potency ratio. The greater oral efficacy of these drugs is due to less first-pass metabolism in the liver. Once absorbed, codeine is metabolized by the liver, and its metabolites are excreted chiefly in the urine, largely in inactive forms. A small fraction (approximately 10%) of administered codeine is *O*-demethylated to form morphine, and both free and conjugated morphine can be found in the urine after therapeutic doses of codeine. Codeine has an exceptionally low affinity for opioid receptors, and the analgesic effect of codeine is due to its conversion to morphine. However, its antitussive actions may involve distinct receptors that bind codeine itself. The half-life of codeine in plasma is 2 to 4 hours.

The conversion of codeine to morphine is effected by the cytochrome P450 enzyme CYP2D6. Well-characterized genetic polymorphisms in CYP2D6 lead to the inability to convert codeine to morphine, thus making codeine ineffective as an analgesic for about 10% of the Caucasian population (Eichelbaum and Evert, 1996). Other polymorphisms can lead to enhanced metabolism and thus increased sensitivity to codeine's effects (Eichelbaum and Evert, 1996). Interestingly, there appears to be variation in metabolic efficiency among different ethnic groups. For example, Chinese produce less morphine from codeine than do Caucasians and also are less sensitive to morphine's effects than are Caucasians (Caraco *et al.*, 1999). The reduced sensitivity to morphine may be due to decreased production of morphine-6-glucuronide (Caraco *et al.*, 1999). Thus, it is important to consider the possibility of metabolic enzyme polymorphism in any patient who does not receive adequate analgesia from codeine or an adequate response to other administered prodrugs.

Tramadol. *Tramadol* (ULTRAM) is a synthetic codeine analog that is a weak μ-opioid receptor agonist. Part of its analgesic effects are produced by inhibition of uptake of norepinephrine and serotonin. Tramadol appears to be as effective as other weak opioids. In the treatment of mild to moderate pain, tramadol is as effective as morphine or meperidine. However, for the treatment of severe or chronic pain, tramadol is less effective. Tramadol is as effective as meperidine in the treatment of labor pain and may cause less neonatal respiratory depression.

Tramadol is 68% bioavailable after a single oral dose and 100% available when administered intramuscularly. Its affinity for the μ opioid receptor is only 1/6000 that of morphine. However, the primary *O*-demethylated metabolite of tramadol is 2- to 4-times as potent as the parent drug and may account for part of the analgesic effect. Tramadol is supplied as a racemic mixture, which is more effective than either enantiomer alone. The (+) enantiomer binds to the μ receptor and inhibits serotonin uptake. The (−) enantiomer inhibits norepinephrine uptake and stimulates α_2-adrenergic receptors (Lewis and Han, 1997). The compound undergoes hepatic metabolism and renal excretion, with an elimination half-life of 6 hours for tramadol and 7.5 hours for its active metabolite. Analgesia begins within an hour of oral dosing, and the effect peaks within 2 to 3 hours. The duration of analgesia is about 6 hours. The maximum recommended daily dose is 400 mg.

Common side effects of tramadol include nausea, vomiting, dizziness, dry mouth, sedation, and headache. Respiratory depression appears to be less than with equianalgesic doses of morphine, and the degree of constipation is less than that seen after equivalent doses of codeine (Duthie, 1998). Tramadol can cause seizures and possibly exacerbate seizures in patients with predisposing factors. While tramadol-induced analgesia is not entirely reversible by naloxone, tramadol-induced respiratory depression can be reversed by naloxone. However, the use of naloxone increases the risk of seizure. Physical dependence on and abuse of tramadol have been reported. Although its abuse potential is unclear, tramadol probably should be avoided in patients with a history of addiction. Because of its inhibitory effect on serotonin uptake, tramadol should not be used in patients taking monoamine oxidase (MAO) inhibitors (Lewis and Han, 1997; *see also* section on interaction of meperidine with other drugs, below).

Heroin. Heroin (diacetylmorphine) is rapidly hydrolyzed to 6-monoacetylmorphine (6-MAM), which, in turn is hydrolyzed to morphine. Both heroin and 6-MAM are more lipid soluble than morphine and enter the brain more readily. Current evidence suggests that morphine and 6-MAM are responsible for the pharmacological actions of heroin. Heroin is mainly excreted in the urine, largely as free and conjugated morphine.

The absorption, fate, and distribution of heroin and other morphine-like drugs have been reviewed by (Misra, 1978) and by (Chan and Matzke, 1987).

Untoward Effects and Precautions. Morphine and related opioids produce a wide spectrum of unwanted effects, including respiratory depression, nausea, vomiting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased pressure in the biliary tract, urinary retention, and hypotension. The bases of these effects have been described above. Rarely, a patient may develop delirium. Increased sensitivity to pain after the analgesia has worn off also may occur.

A number of factors may alter a patient's sensitivity to opioid analgesics, including the integrity of the blood–brain barrier. For example, when morphine is administered to a newborn infant in weight-appropriate doses extrapolated from adults, unexpectedly profound analgesia and respiratory depression may be observed. This is due to the immaturity of the blood–brain barrier in neonates (Way *et al.*, 1965). As mentioned previously, morphine is hydrophilic, so in the normal situation, proportionately less morphine crosses into the CNS than with more lipophilic opioids. In neonates and in other situations with a compromised blood–brain barrier, lipophilic opioids may give

more predictable clinical results than morphine. In adults, the *duration* of the analgesia produced by morphine increases progressively with age; however, the *degree* of analgesia that is obtained with a given dose changes little. Changes in pharmacokinetic parameters only partially explain these observations. The patient with severe pain may tolerate larger doses of morphine. However, as the pain subsides, the patient may exhibit sedation and even respiratory depression as the stimulatory effects of pain are diminished. The reasons for this effect are unclear.

All the opioid analgesics are metabolized by the liver, and the drugs should be used with caution in patients with hepatic disease, since increased bioavailability after oral administration or cumulative effects may occur (*see* Sawe *et al.*, 1981). Renal disease also significantly alters the pharmacokinetics of morphine, codeine, drocode (dihydrocodeine), meperidine, and propoxyphene. Although single doses of morphine are well tolerated, the active metabolite, morphine-6-glucuronide, may accumulate with continued dosing, and symptoms of opioid overdose may result (*see* Chan and Matzke, 1987). This metabolite also may accumulate during repeated administration of codeine to patients with impaired renal function. When repeated doses of meperidine are given to such patients, the accumulation of normeperidine may cause tremor and seizures (Kaiko *et al.*, 1983). Similarly, the repeated administration of propoxyphene may lead to naloxone-insensitive cardiac toxicity caused by the accumulation of norpropoxyphene (*see* Chan and Matzke, 1987).

Morphine and related opioids must be used cautiously in patients with compromised respiratory function, such as those with emphysema, kyphoscoliosis, or severe obesity. In patients with chronic cor pulmonale, death has occurred following therapeutic doses of morphine. Although many patients with such conditions seem to be functioning within normal limits, they are already utilizing compensatory mechanisms, such as increased respiratory rate. Many have chronically elevated levels of plasma CO_2 and may be less sensitive to the stimulating actions of CO_2. The further imposition of the depressant effects of opioids can be disastrous. The respiratory-depressant effects of opioids and the related capacity to elevate intracranial pressure must be considered in the presence of head injury or of an already elevated intracranial pressure. While head injury *per se* does not constitute an absolute contraindication to the use of opioids, the possibility of exaggerated depression of respiration and the potential need to control ventilation of the patient must be considered. Finally, since opioids may produce mental clouding and side effects such as miosis and vomiting, which are important signs in following the clinical course of patients with head injuries, the advisability of their use must be weighed carefully against these risks.

Morphine causes histamine release, which can cause bronchoconstriction and vasodilation. Morphine has the potential to precipitate or exacerbate asthmatic attacks. The use of morphine should be avoided in patients with a history of asthma. Other μ-receptor agonists that do not release histamine, such as the fentanyl derivatives, may be better choices for such patients.

Patients with reduced blood volume are considerably more susceptible to the vasodilatory effects of morphine and related drugs, and these agents must be used cautiously in patients with hypotension from any cause.

Allergic phenomena occur with opioid analgesics, but they are not common. They usually are manifested as urticaria and other types of skin rashes such as fixed eruptions; contact dermatitis in nurses and pharmaceutical workers also occurs. Wheals at the site of injection of morphine, codeine, and related drugs are probably secondary to the release of histamine. Anaphylactoid reactions have been reported after intravenous administration of codeine and morphine, but such reactions are rare. It has been suggested, but not proven, that such reactions are responsible for some of the sudden deaths, episodes of pulmonary edema, and other complications that occur among addicts who use heroin intravenously (*see* Chapter 24).

Interactions with Other Drugs. The depressant effects of some opioids may be exaggerated and prolonged by phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants; the mechanisms of these supraadditive effects are not fully understood but may involve alterations in the rate of metabolic transformation of the opioid or alterations in neurotransmitters involved in the actions of opioids. Some, but not all, phenothiazines reduce the amount of opioid required to produce a given level of analgesia. However, depending on the specific agent, the respiratory-depressant effects also seem to be enhanced, the degree of sedation is increased, and the hypotensive effects of phenothiazines become an additional complication. Some phenothiazine derivatives enhance the sedative effects, but at the same time seem to be antianalgesic and increase the amount of opioid required to produce satisfactory relief from pain. Small doses of amphetamine substantially increase the analgesic and euphoriant effects of morphine and may decrease its sedative side effects. A number of antihistamines exhibit modest analgesic actions; some (*e.g.*, hydroxyzine) enhance the analgesic effects of low doses of opioids (Rumore and Schlichting, 1986). Antidepressants such as desipramine and amitriptyline are used in the treatment of chronic neuropathic pain but have limited intrinsic analgesic actions in acute pain. However, antidepressants may enhance morphine-induced analgesia (Levine *et al.*, 1986; Pick *et al.*, 1992b). The analgesic synergism between opioids and aspirin-like drugs is discussed below and in Chapter 27.

OTHER μ-RECEPTOR AGONISTS

Levorphanol and Congeners

Levorphanol (LEVO-DROMORAN) is the only commercially available opioid agonist of the morphinan series. The *d*-isomer (dextrorphan) is relatively devoid of analgesic action but may have inhibitory effects at NMDA receptors. The structure of levorphanol is shown in Table 23–5.

The pharmacological effects of levorphanol closely parallel those of morphine. However, clinical reports suggest that it may produce less nausea and vomiting. Although levorphanol is less effective when given orally, its oral–parenteral potency ratio is comparable to that of codeine and oxycodone. The average adult dose (2 mg subcutaneously) produces analgesia for a period of time somewhat longer than that for morphine. Levorphanol is metabolized less rapidly and has a half-life of about 12 to 16 hours; repeated administration at short intervals may thus lead to accumulation of the drug in plasma (Foley, 1985).

Meperidine and Congeners

The structural formulas of *meperidine,* a *phenylpiperidine,* and some of its congeners are shown in Figure 23–4. Meperidine is predominantly a μ-receptor agonist, and it exerts its chief pharmacological action on the CNS and the neural elements in the bowel. The use of meperidine has diminished in recent years due to concerns over metabolite toxicity. For this reason, meperidine is no longer recommended for the treatment of chronic pain and should not be used for longer than 48 hours or in doses greater than 600 mg/24 hrs (Agency for Health Care Policy and Research, 1992).

Pharmacological Properties. ***Central Nervous System.*** Meperidine produces a pattern of effects similar but not identical to that described for morphine.

Analgesia. The analgesic effects of meperidine are detectable about 15 minutes after oral administration, reach a peak in about 1 to 2 hours, and subside gradually. The onset of analgesic effect is faster (within 10 minutes) after subcutaneous or intramuscular administration, and the effect reaches a peak in about 1 hour that corresponds closely to peak concentrations in plasma. In clinical use, the duration of effective analgesia is approximately 1.5 to 3 hours. In general, 75 to 100 mg of *meperidine hydrochloride* (*pethidine,* DEMEROL) given parenterally is approximately equivalent to 10 mg of morphine, and, in equianalgesic doses, meperidine produces as much sedation, respiratory depression, and euphoria as does morphine. In terms of total analgesic effect, meperidine is about one-third as effective when given by mouth as when administered parenterally. A few patients may experience dysphoria.

Other CNS Actions. Peak respiratory depression is observed within 1 hour after intramuscular administration, and there is a return toward normal starting at about 2 hours. Like other opioids, meperidine causes pupillary constriction, increases the sensitivity of the labyrinthine apparatus, and has effects on the secretion of pituitary hormones similar to those of morphine. Meperidine sometimes causes CNS excitation, characterized by tremors, muscle twitches, and seizures; these effects are due largely to accumulation of a metabolite, normeperidine (*see* below). As with morphine, respiratory depression is responsible for an accumulation of CO_2, which, in turn, leads to cerebrovascular dilation, increase in cerebral blood flow, and elevation of cerebrospinal fluid pressure.

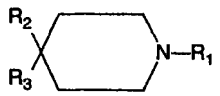
Cardiovascular System. The effects of meperidine on the cardiovascular system generally resemble those of morphine, including the ability to release histamine upon parenteral administration (Lee *et al.,* 1976). Intramuscular administration of meperidine does not significantly affect heart rate, but intravenous administration frequently produces a marked increase in heart rate.

Smooth Muscle. Meperidine has effects on certain smooth muscles qualitatively similar to those observed with other opioids. Meperidine does not cause as much constipation as does morphine even when given over prolonged periods of time; this may be related to its greater ability to enter the CNS, thereby producing analgesia at lower systemic concentrations. As with other opioids, clinical doses of meperidine slow gastric emptying sufficiently to delay absorption of other drugs significantly.

The uterus of a nonpregnant woman usually is mildly stimulated by meperidine. Administered prior to an oxytocic, meperidine does not exert any antagonistic effect. Therapeutic doses given during active labor do not delay the birth process; in fact, the frequency, duration, and amplitude of uterine contraction sometimes may be increased (Zimmer *et al.,* 1988). The drug does not interfere with normal postpartum contraction or involution of the uterus, and it does not increase the incidence of postpartum hemorrhage.

Absorption, Fate, and Excretion. Meperidine is absorbed by all routes of administration, but the rate of absorption may be erratic after intramuscular injection. The peak plasma concentration usually occurs at about 45 minutes, but the range is wide. After oral administration, only about 50% of the drug escapes first-pass metabolism to enter the circulation, and peak concentrations in plasma are usually observed in 1 to 2 hours (Herman *et al.,* 1985).

Meperidine is metabolized chiefly in the liver, with a half-life of about 3 hours. In patients with cirrhosis, the



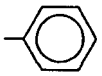
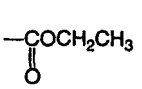
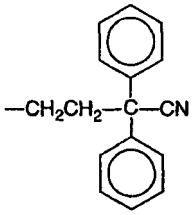
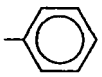
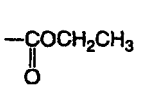
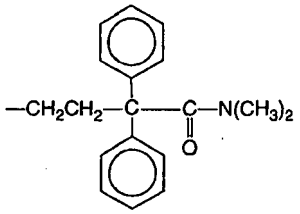
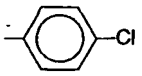
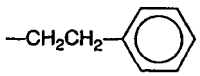
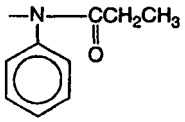
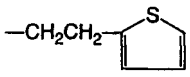
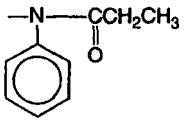
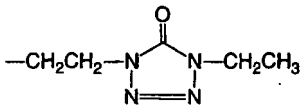
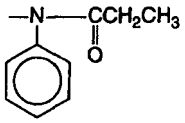
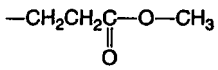
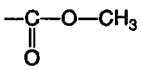
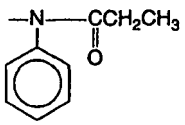
COMPOUND	R_1	R_2	R_3
Meperidine	$-CH_3$		
Diphenoxylate			
Loperamide			—OH
Fentanyl		—H	
Sufentanil		$-CH_2OCH_3$	
Alfentanil		$-CH_2OCH_3$	
Remifentanil			

Figure 23–4. Chemical structures of piperidine and phenylpiperidine analgesics.

bioavailability of meperidine is increased to as much as 80%, and the half-lives of both meperidine and normeperidine are prolonged. Approximately 60% of meperidine in plasma is protein bound.

In human beings, meperidine is hydrolyzed to meperidinic acid, which, in turn, is partially conjugated. Meperidine also is *N*-demethylated to normeperidine, which may then be hydrolyzed to normeperidinic acid and subsequently

conjugated. The clinical significance of the formation of normeperidine is discussed further below. Only a small amount of meperidine is excreted unchanged.

Untoward Effects, Precautions, and Contraindications. The pattern and overall incidence of untoward effects that follow the use of meperidine are similar to those observed after equianalgesic doses of morphine, except that constipation and urinary retention may be less common. Patients who experience nausea and vomiting with morphine may not do so with meperidine; the converse also may be true. As with other opioids, tolerance develops to some of these effects. The contraindications are generally the same as for other opioids. In patients or addicts who are tolerant to the depressant effects of meperidine, large doses repeated at short intervals may produce an excitatory syndrome including hallucinations, tremors, muscle twitches, dilated pupils, hyperactive reflexes, and convulsions. These excitatory symptoms are due to the accumulation of normeperidine, which has a half-life of 15 to 20 hours compared with 3 hours for meperidine. Opioid antagonists can block the convulsant effect of normeperidine in the mouse. Since normeperidine is eliminated by both the kidney and the liver, decreased renal or hepatic function increases the likelihood of such toxicity (Kaiko *et al.*, 1983). Thus, meperidine is not the drug of choice for the treatment of severe or prolonged pain because of its shorter duration of action relative to morphine and the potential for CNS toxicity from normeperidine.

Interaction with Other Drugs. Severe reactions may follow the administration of meperidine to patients being treated with MAO inhibitors. Two basic types of interactions can be observed. The most prominent is an excitatory reaction with delirium, hyperthermia, headache, hyper- or hypotension, rigidity, convulsions, coma, and death. This reaction may be due to the ability of meperidine to block neuronal reuptake of serotonin and the resultant serotonergic overactivity (Stack *et al.*, 1988). Therefore, meperidine and its congeners should not be used in patients taking MAO inhibitors. Dextromethorphan also inhibits neuronal serotonin uptake and should be avoided in these patients. As discussed above, tramadol inhibits uptake of norepinephrine and serotonin and should not be used concomitantly with MAO inhibitors. Similar interactions with other currently used opioids have not been observed clinically. Another type of interaction, a potentiation of opioid effect due to inhibition of hepatic microsomal enzymes, also can be observed in patients taking MAO inhibitors, necessitating a reduction in the doses of opioids.

Chlorpromazine increases the respiratory-depressant effects of meperidine, as do tricyclic antidepressants; this is not true of diazepam. Concurrent administration of drugs such as promethazine or chlorpromazine also may greatly enhance meperidine-induced sedation without slowing clearance of the drug. Treatment with phenobarbital or phenytoin increases systemic clearance and decreases oral bioavailability of meperidine; this is associated with an elevation of the concentration of normeperidine in plasma (Edwards *et al.*, 1982). As with morphine, concomitant administration of amphetamine has been reported to enhance the analgesic effects of meperidine and its congeners while counteracting sedation.

Therapeutic Uses. The major use of meperidine is for analgesia. Unlike morphine and its congeners, meperidine is not used for the treatment of cough or diarrhea. Single doses of meperidine also appear to be effective in the treatment of postanesthetic shivering.

Meperidine crosses the placental barrier and even in reasonable analgesic doses causes a significant increase in the percentage of babies who show delayed respiration, decreased respiratory minute volume, or decreased oxygen saturation, or who require resuscitation. Both fetal and maternal respiratory depression induced by meperidine can be treated with naloxone. The fraction of drug that is bound to protein is lower in the fetus; concentrations of free drug thus may be considerably higher than in the mother. Nevertheless, meperidine produces less respiratory depression in the newborn than does an equianalgesic dose of morphine or methadone (Fishburne, 1982).

Congeners of Meperidine. ***Diphenoxylate.*** *Diphenoxylate* is a meperidine congener that has a definite constipating effect in human beings. Its only approved use is in the treatment of diarrhea. Although single doses in the therapeutic range (*see* below) produce little or no morphine-like subjective effects, at high doses (40 to 60 mg) the drug shows typical opioid activity, including euphoria, suppression of morphine abstinence, and a morphine-like physical dependence after chronic administration. Diphenoxylate is unusual in that even its salts are virtually insoluble in aqueous solution, thus obviating the possibility of abuse by the parenteral route. *Diphenoxylate hydrochloride* is available only in combination with atropine sulfate (LOMOTIL, others). The recommended daily dosage of diphenoxylate for treatment of diarrhea in adults is 20 mg, in divided doses. *Difenoxin* (difenoxylic acid; MOTOFEN) is one of the metabolites of diphenoxylate; it has actions similar to those of the parent compound.

Loperamide. Loperamide (IMODIUM, others), like diphenoxylate, is a piperidine derivative (*see* Figure 23–3). It slows gastrointestinal motility by effects on the circular and longitudinal muscles of the intestine, presumably as a result of its interactions with opioid receptors in the intestine. Some part of its antidiarrheal effect may be due to a reduction of gastrointestinal secretion (*see* above; *see also* Manara and Bianchetti, 1985; Coupar, 1987; Kromer, 1988). In controlling chronic diarrhea, loperamide is as effective as diphenoxylate. In clinical studies, the most common side effect is abdominal cramps. Little tolerance develops to its constipating effect.

In human volunteers taking large doses of loperamide, concentrations of drug in plasma peak about 4 hours after ingestion; this long latency may be due to inhibition of gastrointestinal motility and to enterohepatic circulation of the drug. The apparent elimination half-life is 7 to 14 hours. Loperamide is not well absorbed after oral administration and, in addition,

apparently does not penetrate well into the brain because of exclusion by a P-glycoprotein transporter widely expressed in the blood–brain barrier (Sadeque *et al.*, 2000). Mice with deletions of one of the genes encoding the P-glycoprotein transporter have much higher brain levels and significant central effects after administration of loperamide (Schinkel *et al.*, 1996). Inhibition of P-glycoprotein by many clinically used drugs, such as quinidine, verapamil, and ketoconazole, possibly could lead to enhanced central effects of loperamide.

In general, loperamide is unlikely to be abused parenterally because of its low solubility; large doses of loperamide given to human volunteers do not elicit pleasurable effects typical of opioids. The usual dosage is 4 to 8 mg per day; the daily dose should not exceed 16 mg.

Fentanyl and Congeners

Fentanyl is a synthetic opioid related to the phenylpiperidines (*see* Figure 23–3). It is a μ-receptor agonist and is about 100-times more potent than morphine as an analgesic.

The actions of fentanyl and its congeners, *sufentanil, alfentanil,* and *remifentanil,* are similar to those of other μ-receptor agonists. Fentanyl is a popular drug in anesthetic practice because of its shorter time to peak analgesic effect, rapid termination of effect after small bolus doses, and relative cardiovascular stability (*see* Chapter 14).

Pharmacological Properties. ***Analgesia.*** The analgesic effects of fentanyl and sufentanil are similar to those of morphine and other μ opioids. Fentanyl is approximately 100-times more potent than morphine, and sufentanil is approximately 1000-times more potent than morphine. These drugs are most commonly administered intravenously, although both also are commonly administered epidurally and intrathecally for acute postoperative and chronic pain management. Fentanyl and sufentanil are far more lipid soluble than morphine; thus the risk of delayed respiratory depression due to rostral spread of intraspinally administered narcotic to respiratory centers is greatly reduced. The time to peak analgesic effect after intravenous administration of fentanyl and sufentanil is less than that for morphine and meperidine, with peak analgesia being reached after about 5 minutes, as opposed to approximately 15 minutes. Recovery from analgesic effects also occurs more quickly. However, with larger doses or prolonged infusions, the effects of these drugs become more long lasting, with durations of action becoming similar to those of longer acting opioids (*see* below).

Other CNS Effects. As with other μ opioids, nausea, vomiting, and itching can be observed with fentanyl. Muscle rigidity, while possible after all narcotics, appears to be more common after administration of bolus doses of fentanyl or its congeners. This effect is felt to be centrally mediated and may be due in part to their increased potency relative to morphine. Rigidity can be mitigated by avoiding bolus dosing, slower administration of boluses, and by pretreatment with a nonopioid anesthetic induction agent. Rigidity can be treated with depolarizing or nondepolarizing neuromuscular blocking agents while controlling the patient's ventilation. Care must be taken to make sure the patient is not aware but unable to move. Respiratory depression is similar to that observed with other μ-receptor agonists, but the onset is more rapid. As with analgesia, respiratory depression after small doses is of shorter duration than with morphine, but of similar duration after large doses or long infusions. As with morphine and meperidine, delayed respiratory depression also can be seen after the use of fentanyl, sufentanil, or alfentanil, possibly due to enterohepatic circulation. High doses of fentanyl can cause neuroexcitation and, rarely, seizure-like activity in human beings (Bailey and Stanley, 1994). Fentanyl has minimal effects on intracranial pressure when ventilation is controlled and the arterial CO_2 concentration is not allowed to rise.

Cardiovascular System. Fentanyl and its derivatives decrease the heart rate and can mildly decrease blood pressure. However, these drugs do not release histamine and in general provide a marked degree of cardiovascular stability. Direct depressant effects on the myocardium are minimal. For this reason, high doses of fentanyl or sufentanil commonly are used as the primary anesthetic for patients undergoing cardiovascular surgery or for patients with poor cardiac function.

Absorption, Fate, and Excretion. These agents are highly lipid soluble and rapidly cross the blood–brain barrier. This is reflected in the half-life for equilibration between the plasma and CSF of approximately 5 minutes for fentanyl and sufentanil. The levels in plasma and CSF rapidly decline due to redistribution of fentanyl from highly perfused tissue groups to other tissues, such as muscle and fat. As saturation of less-well-perfused tissue occurs, the duration of fentanyl's and sufentanil's effects approach the length of their elimination half lives of between 3 and 4 hours (Sanford and Gutstein, 1995). Fentanyl and sufentanil undergo hepatic metabolism and renal excretion. Therefore, with the use of higher doses or prolonged infusions, fentanyl and sufentanil become longer acting.

Therapeutic Uses. *Fentanyl citrate* (SUBLIMAZE) and *sufentanil citrate* (SUFENTA) have gained widespread popularity as anesthetic adjuvants (*see* Chapter 14). They commonly are used either intravenously, epidurally, or

intrathecally. A formulation of fentanyl and *droperidol* (INNOVAR) was commonly used for anesthesia. However, dysphoric side effects of droperidol have limited the popularity of this combination. Epidural use of fentanyl and sufentanil for postoperative or labor analgesia has gained increasing popularity. A combination of epidural opioids with local anesthetics permits reduction in the dosage of both components, minimizing the side effects of both local anesthetics (*i.e.,* motor blockade) and opioids (*i.e.,* urinary retention, itching, and delayed respiratory depression in the case of morphine). Intravenous use of fentanyl and sufentanil for postoperative pain has been effective but limited by clinical concerns about muscle rigidity. However, the use of fentanyl and sufentanil in chronic pain treatment has become more widespread. Epidural and intrathecal infusions, both with and without local anesthetic, are used in the management of chronic malignant pain and selected cases of nonmalignant pain. Also, the development of novel, less invasive routes of administration for fentanyl has facilitated the use of these compounds in chronic pain management. Transdermal patches (DURAGESIC) that provide sustained release of fentanyl for 48 hours or more are available. However, factors promoting increased absorption (*e.g.,* fever) can lead to relative overdosage and increased side effects (*see also* the section on alternative routes of administration, below). Also, the FENTANYL ORALET, a formulation that permits rapid absorption of fentanyl through the buccal mucosa (much like a lollipop), was tried as an anesthetic premedicant but did not gain wide acceptance due to undesirable side effects in opioid-naïve patients (nausea, vomiting, pruritus, and respiratory depression). A similar fentanyl product, ACTIQ, is available in higher strengths and is used for relief of breakthrough cancer pain (Ashburn *et al.,* 1989).

Alfentanil and Remifentanil. These compounds were developed in an effort to create analgesics with a more rapid onset and predictable termination of opioid effects. The potency of remifentanil is approximately equal to that of fentanyl and is between 20- and 30-times greater than that of alfentanil. The pharmacological properties of alfentanil and remifentanil are similar to those of fentanyl and sufentanil. They have similar incidences of nausea, vomiting, and dose-dependent muscle rigidity. Nausea, vomiting, itching, and headaches have been reported when remifentanil has been used for conscious analgesia for painful procedures. Intracranial pressure changes are minimal when ventilation is controlled. Seizures after remifentanil administration have not yet been reported.

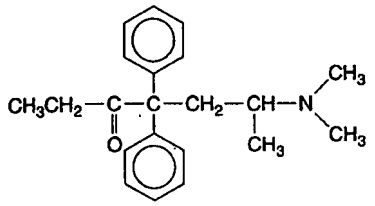
Absorption, Fate and Excretion. Both alfentanil and remifentanil have a more rapid onset of analgesic action than do fentanyl on sufentanil. Analgesic effects occur within of 1 to 1.5 minutes. After intravenous administration, alfentanil is metabolized in the liver similarly to fentanyl and sufentanil, with an elimination half-life of 1 to 2 hours. The duration of action of alfentanil is dependent on both the dose and length of administration. Remifentanil is unique in that it is metabolized by plasma esterases (Burkle *et al.,* 1996). Elimination is independent of hepatic metabolism or renal excretion, and the elimination half-life is 8 to 20 minutes. There is no prolongation of effect with repeated dosing or prolonged infusion. Age and weight can affect clearance of remifentanil, requiring that dosage be reduced in the elderly and based on lean body mass. However, neither of these conditions causes major changes in duration of effect. After 3- to 5-hour infusions of remifentanil, recovery of respiratory function can be seen within 3 to 5 minutes, while full recovery from all effects of remifentanil is observed within 15 minutes (Glass *et al.,* 1999). The primary metabolite, remifentanil acid, is 2000- to 4000-times less potent than remifentanil and is renally excreted. Peak respiratory depression after bolus doses of remifentanil occurs after 5 minutes (Patel and Spencer, 1996).

Therapeutic Uses. *Alfentanil hydrochloride* (ALFENTA) and *remifentanil hydrochloride* (ULTIVA) are useful for short, painful procedures that require intense analgesia and blunting of stress responses. The titratability of remifentanil and its consistent, rapid offset make it ideally suited for short surgical procedures where rapid recovery is an issue. Remifentanil also has been used successfully for longer neurosurgical procedures, where rapid emergence from anesthesia is important. However, in cases where postprocedural analgesia is required, remifentanil alone is a poor choice. In this situation, either a longer-acting opioid or another analgesic modality should be combined with remifentanil for prolonged analgesia, or another opioid should be used. Alfentanil has been administered intraspinally for pain control. Remifentanil is presently not used intraspinally, as glycine in the drug vehicle can cause temporary motor paralysis. It is generally given by continuous intravenous infusion, as its short duration of action makes bolus administration impractical.

Methadone and Congeners

Methadone is a long-lasting μ-receptor agonist with pharmacological properties qualitatively similar to those of morphine.

Chemistry. Methadone has the following structural formula:



METHADONE

The analgesic activity of the racemate is almost entirely the result of its content of *l*-methadone, which is 8- to 50-times more potent than the *d* isomer; *d*-methadone also lacks significant respiratory depressant action and addiction liability, but it does possess antitussive activity.

Pharmacological Actions. The outstanding properties of methadone are its analgesic activity, its efficacy by the oral route, its extended duration of action in suppressing withdrawal symptoms in physically dependent individuals, and its tendency to show persistent effects with repeated administration. Miotic and respiratory-depressant effects can be detected for more than 24 hours after a single dose and, upon repeated administration, marked sedation is seen in some patients. Effects on cough, bowel motility, biliary tone, and the secretion of pituitary hormones are qualitatively similar to those of morphine.

Absorption, Fate, and Excretion. Methadone is well absorbed from the gastrointestinal tract and can be detected in plasma within 30 minutes after oral ingestion; it reaches peak concentrations at about 4 hours. After therapeutic doses, about 90% of methadone is bound to plasma proteins. Peak concentrations occur in the brain within 1 or 2 hours after subcutaneous or intramuscular administration, and this correlates well with the intensity and duration of analgesia. Methadone also can be absorbed from the buccal mucosa (Weinberg *et al.,* 1988).

Methadone undergoes extensive biotransformation in the liver. The major metabolites, the results of *N*-demethylation and cyclization to form pyrrolidines and pyrroline, are excreted in the urine and the bile along with small amounts of unchanged drug. The amount of methadone excreted in the urine is increased when the urine is acidified. The half-life of methadone is approximately 15 to 40 hours.

Methadone appears to be firmly bound to protein in various tissues, including brain. After repeated administration there is gradual accumulation in tissues. When administration is discontinued, low concentrations are maintained in plasma by slow release from extravascular binding sites (*see* Kreek, 1979); this process probably accounts for the relatively mild but protracted withdrawal syndrome.

Side Effects, Toxicity, Drug Interactions, and Precautions. Side effects, toxicity, and conditions that alter sensitivity, as well as the treatment of acute intoxication, are similar to those described for morphine. During long-term administration, there may be excessive sweating, lymphocytosis, and increased concentrations of prolactin, albumin, and globulins in the plasma. Rifampin and phenytoin accelerate the metabolism of methadone and can precipitate withdrawal symptoms (*see* Kreek, 1979).

Tolerance and Physical Dependence. Volunteer postaddicts who receive subcutaneous or oral methadone daily develop partial tolerance to the nauseant, anorectic, miotic sedative, respiratory-depressant, and cardiovascular effects of methadone. Tolerance develops more slowly to methadone than to morphine in some patients, especially with respect to the depressant effects. However, this may be related in part to cumulative effects of the drug or its metabolites. Tolerance to the constipating effect of methadone does not develop as fully as does tolerance to other effects. The behavior of addicts who use methadone parenterally is strikingly similar to that of morphine addicts, but many former heroin users treated with oral methadone show virtually no overt behavioral effects.

Development of physical dependence during the long-term administration of methadone can be demonstrated by drug withdrawal or by administration of an opioid antagonist. Subcutaneous administration of 10 to 20 mg of methadone to former opioid addicts produces definite euphoria equal in duration to that caused by morphine, and its overall abuse potential is comparable to that of morphine.

Therapeutic Uses. The primary uses of *methadone hydrochloride* (DOLOPHINE, others) are relief of chronic pain, treatment of opioid abstinence syndromes, and treatment of heroin users. It is not widely used as an antiperistaltic agent. It should not be used in labor.

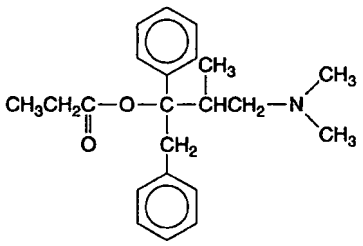
Analgesia. The onset of analgesia occurs 10 to 20 minutes following parenteral administration and 30 to 60 minutes after oral medication. The average minimal effective analgesic concentration in blood is about 30 ng/ml (Gourlay *et al.,* 1986). The typical oral dose is 2.5 to 15 mg, depending on the severity of the pain and the response of the patient. The initial parenteral dose is usually 2.5 to 10 mg. Care must be taken when escalating the dosage, because of the prolonged half-life of the drug and its tendency to accumulate over a period of several days with repeated dosing. Despite its longer plasma half-life, the duration of the analgesic action of single doses is essentially the same as that of morphine. With repeated usage, cumulative effects are seen, so that either lower dosage or longer intervals between doses become possible. In contrast to morphine, methadone and many of its congeners retain a considerable degree of their effectiveness when given orally. In terms of total analgesic effects, methadone given orally is about 50% as effective as the same dose administered intramuscularly; however, the oral-parenteral

potency ratio is considerably lower when peak analgesic effect is considered. In equianalgesic doses, the pattern and incidence of untoward effects caused by methadone and morphine are similar.

Levomethadyl Acetate. *Levomethadyl acetate* (*l*-α-acetylmethadol; ORLAAM) is a congener of methadone that is approved for use in maintenance programs for the treatment of heroin addicts. The drug is thought to act, in part, by its conversion to active metabolites, which explains its slow onset and protracted duration of action. The slow onset of effect can be problematic in the treatment of addicts (*see* Chapter 24). In physically dependent subjects taking levomethadyl acetate, withdrawal symptoms are not perceived for 72 to 96 hours after the last oral dose. Most subjects are comfortable taking a single dose as infrequently as every 72 hours (*see* Ling *et al.*, 1978). The *d* isomer of methadyl acetate is inactive.

Propoxyphene

Propoxyphene is structurally related to methadone (*see* below). Its analgesic effect resides in the dextro isomer, *d*-propoxyphene (dextropropoxyphene). However, levopropoxyphene seems to have some antitussive activity. The structure of propoxyphene is shown below.



PROPOXYPHENE

Pharmacological Actions. Although slightly less selective than morphine, propoxyphene binds primarily to μ-opioid receptors and produces analgesia and other CNS effects that are similar to those seen with morphine-like opioids. It is likely that at equianalgesic doses the incidence of side effects such as nausea, anorexia, constipation, abdominal pain, and drowsiness would be similar to those of codeine.

As an analgesic, propoxyphene is about one-half to two-thirds as potent as codeine given orally. Ninety to 120 mg of propoxyphene hydrochloride administered orally would equal the analgesic effects of 60 mg of codeine, a dose that usually produces about as much analgesia as 600 mg of aspirin. Combinations of propoxyphene and aspirin, like combinations of codeine and aspirin, afford a higher level of analgesia than does either agent given alone (Beaver, 1988).

Absorption, Fate, and Excretion. Following oral administration, concentrations of propoxyphene in plasma reach their highest values at 1 to 2 hours. There is great variability between subjects in the rate of clearance and the plasma concentrations that are achieved. The average half-life of propoxyphene in plasma after a single dose is from 6 to 12 hours, which is longer than that of codeine. In human beings, the major route of metabolism is *N*-demethylation to yield norpropoxyphene. The half-life of norpropoxyphene is about 30 hours, and its accumulation with repeated doses may be responsible for some of the observed toxicity (*see* Chan and Matzke, 1987).

Toxicity. Given orally, propoxyphene is approximately one-third as potent as orally administered codeine in depressing respiration. Moderately toxic doses usually produce CNS and respiratory depression, but with still-larger doses the clinical picture may be complicated by convulsions in addition to respiratory depression. Delusions, hallucinations, confusion, cardiotoxicity, and pulmonary edema also have been noted. Respiratory-depressant effects are significantly enhanced when ethanol or sedative-hypnotics are ingested concurrently. Naloxone antagonizes the respiratory-depressant, convulsant, and some of the cardiotoxic effects of propoxyphene.

Tolerance and Dependence. Very large doses [800 mg of *propoxyphene hydrochloride* (DARVON, others) or 1200 mg of the napsylate (DARVON-N) per day] reduce the intensity of the morphine withdrawal syndrome somewhat less effectively than do 1500-mg doses of codeine. Maximal tolerated doses are equivalent to daily doses of 20 to 25 mg of morphine, given subcutaneously. The use of higher doses of propoxyphene is prevented by untoward side effects and the occurrence of toxic psychoses. Very large doses produce some respiratory depression in morphine-tolerant addicts, suggesting that cross-tolerance between propoxyphene and morphine is incomplete. Abrupt discontinuation of chronically administered propoxyphene hydrochloride (up to 800 mg per day, given for almost 2 months) results in mild abstinence phenomena, and large oral doses (300 to 600 mg) produce subjective effects that are considered pleasurable by postaddicts. The drug is quite irritating when administered either intravenously or subcutaneously, so that abuse by these routes results in severe damage to veins and soft tissues.

Therapeutic Uses. Propoxyphene is recommended for the treatment of mild-to-moderate pain. Given acutely, the commonly prescribed combination of 32 mg of propoxyphene with aspirin may not produce more analgesia than aspirin alone, and doses of 65 mg of the hydrochloride or 100 mg of the napsylate are suggested. Propoxyphene is most often given in combination with aspirin or acetaminophen. The wide popularity of propoxyphene in clinical situations in which codeine was once used is largely a result of unrealistic overconcern about the addictive potential of codeine.

ACUTE OPIOID TOXICITY

Acute opioid toxicity may result from clinical overdosage, accidental overdosage in addicts, or attempts at suicide. Occasionally, a delayed type of toxicity may occur from the injection of an opioid into chilled skin areas or in patients with low blood pressure and shock. The drug is not fully absorbed, and, therefore, a subsequent dose may be given. When normal circulation is established, an excessive amount may be absorbed suddenly. It is difficult to define the exact amount of any opioid that is toxic or lethal to human beings. Recent experiences with

methadone indicate that, in nontolerant individuals, serious toxicity may follow the oral ingestion of 40 to 60 mg. Older literature suggests that, in the case of morphine, a normal, pain-free adult is not likely to die after oral doses of less than 120 mg or to have serious toxicity with less than 30 mg parenterally.

Symptoms and Diagnosis. The patient who has taken an overdose of an opioid usually is stuporous or, if a large overdose has been taken, may be in a profound coma. The respiratory rate will be very low or the patient may be apneic, and cyanosis may be present. As respiratory exchange decreases, blood pressure, at first likely to be near normal, will fall progressively. If adequate oxygenation is restored early, the blood pressure will improve; if hypoxia persists untreated, there may be capillary damage, and measures to combat shock may be required. The pupils will be symmetrical and pinpoint in size; however, if hypoxia is severe, they may be dilated. Urine formation is depressed. Body temperature falls, and the skin becomes cold and clammy. The skeletal muscles are flaccid, the jaw is relaxed, and the tongue may fall back and block the airway. Frank convulsions occasionally may be noted in infants and children. When death occurs, it is nearly always due to respiratory failure. Even if respiration is restored, death still may occur as a result of complications that develop during the period of coma, such as pneumonia or shock. Noncardiogenic pulmonary edema is seen commonly with opioid poisoning. It probably is not due to contaminants or to anaphylactoid reactions, and it has been observed following toxic doses of morphine, methadone, propoxyphene, and uncontaminated heroin.

The triad of coma, pinpoint pupils, and depressed respiration strongly suggests opioid poisoning. The finding of needle marks suggestive of addiction further supports the diagnosis. Mixed poisonings, however, are not uncommon. Examination of the urine and gastric contents for drugs may aid in diagnosis, but the results usually become available too late to influence treatment.

Treatment. The first step is to establish a patent airway and ventilate the patient. Opioid antagonists (*see* below) can produce dramatic reversal of the severe respiratory depression, and the antagonist *naloxone* (*see* below) is the treatment of choice. However, care should be taken to avoid precipitating withdrawal in dependent patients, who may be extremely sensitive to antagonists. The safest approach is to dilute the standard naloxone dose (0.4 mg) and slowly administer it intravenously, monitoring arousal and respiratory function. With care, it usually is possible to reverse the respiratory depression without precipitating a major withdrawal syndrome. If no response is seen with the first dose, additional doses can be given. Patients should be observed for rebound increases in sympathetic nervous system activity, which may result in cardiac arrhythmias and pulmonary edema (*see* Duthie and Nimmo, 1987). For reversing opioid poisoning in children, the initial dose of naloxone is 0.01 mg/kg. If no effect is seen after a total dose of 10 mg, one can reasonably question the accuracy of the diagnosis. Pulmonary edema sometimes associated with opioid overdosage may be countered by positive-pressure respiration. Tonic-clonic seizures, occasionally seen as part of the toxic syndrome with meperidine and propoxyphene, are ameliorated by treatment with naloxone.

The presence of general CNS depressants does not prevent the salutary effect of naloxone, and in cases of mixed intoxications, the situation will be improved largely due to antagonism of the respiratory-depressant effects of the opioid. However, some evidence indicates that naloxone and naltrexone also may antagonize some of the depressant actions of sedative-hypnotics (*see* below). One need not attempt to restore the patient to full consciousness. The duration of action of the available antagonists is shorter than that of many opioids; hence, patients must be watched carefully, lest they slip back into coma. This is particularly important when the overdosage is due to methadone or *l*-acetylmethadol. The depressant effects of these drugs may persist for 24 to 72 hours, and fatalities have occurred as a result of premature discontinuation of naloxone. In cases of overdoses of these drugs, a continuous infusion of naloxone should be considered. Toxicity due to overdose of pentazocine and other opioids with mixed actions may require higher doses of naloxone. The pharmacological actions of opioid antagonists are discussed in more detail below.

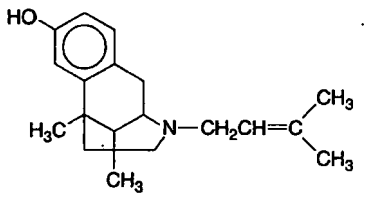
OPIOID AGONIST/ANTAGONISTS AND PARTIAL AGONISTS

The drugs described in this section differ from clinically used μ-opioid receptor agonists. Drugs such as *nalbuphine* and *butorphanol* are competitive μ-receptor antagonists but exert their analgesic actions by acting as agonists at κ receptors. *Pentazocine* qualitatively resembles these drugs, but it may be a weaker μ-receptor antagonist or partial agonist while retaining its κ-agonist activity. *Buprenorphine,* on the other hand, is a partial agonist at μ receptors. The stimulus for the development of mixed agonist/antagonist drugs was a need for analgesics with less respiratory depression and addictive potential. Currently, the clinical use of these compounds is limited by undesirable side effects and by limited analgesic effects.

Pentazocine

Pentazocine was synthesized as part of a deliberate effort to develop an effective analgesic with little or no abuse potential. It has both agonistic actions and weak opioid antagonistic activity. The pharmacology of pentazocine has been reviewed by (Brogden *et al.,* 1973).

Chemistry. Pentazocine is a benzomorphan derivative with the following structural formula:



PENTAZOCINE

The compound has a large substituent on the nitrogen atom that is analogous to position 17 of morphine. This structural feature is common to a number of opioids with antagonist or agonist/antagonist activity. The analgesic and respiratory-depressant activity of the racemate is due mainly to the *l* isomer.

Pharmacological Actions. The pattern of CNS effects produced by pentazocine is generally similar to that of the morphine-like opioids, including analgesia, sedation, and respiratory depression. The analgesic effects of pentazocine are due to agonistic actions at κ-opioid receptors. Higher doses of pentazocine (60 to 90 mg) elicit dysphoric and psychotomimetic effects. The mechanisms responsible for these side effects are not known but might involve activation of supraspinal κ receptors, since it has been suggested that these untoward effects may be reversible by naloxone.

The cardiovascular responses to pentazocine differ from those seen with typical μ-receptor agonists, in that high doses cause an increase in blood pressure and heart rate. In patients with coronary artery disease, pentazocine administered intravenously elevates mean aortic pressure, left ventricular end-diastolic pressure, and mean pulmonary artery pressure and causes an increase in cardiac work (Alderman *et al.*, 1972; Lee *et al.*, 1976). A rise in the concentrations of catecholamines in plasma may account for its effects on blood pressure.

Pentazocine acts as a weak antagonist or partial agonist at μ-opioid receptors. Low doses (20 mg given parenterally) depress respiration as much as does 10 mg of morphine, but increasing the pentazocine dose does not produce a proportionate increase in respiratory depression. Pentazocine does not antagonize the respiratory depression produced by morphine. However, when given to patients dependent on morphine or other μ-receptor agonists, pentazocine may precipitate withdrawal. In patients tolerant to morphine-like opioids, pentazocine reduces the analgesia produced by their administration, even when clear-cut withdrawal symptoms are not precipitated. Ceiling effects for both analgesia and respiratory depression are observed above 50 to 100 mg of pentazocine (Bailey and Stanley, 1994).

Absorption, Fate, and Excretion. Pentazocine is well absorbed from the gastrointestinal tract and from subcutaneous and intramuscular sites. Peak analgesia occurs 15 minutes to 1 hour after intramuscular administration and 1 to 3 hours after oral administration. The half-life in plasma is 4 to 5 hours. First-pass metabolism in the liver is extensive, and somewhat less than 20% of pentazocine enters the systemic circulation. Drug action is terminated by hepatic metabolism and renal excretion.

Side Effects, Toxicity, and Precautions. The most commonly reported untoward effects are sedation, sweating, and dizziness or lightheadedness; nausea also occurs, but vomiting is less common than with morphine. Psychotomimetic effects, such as uncontrollable or weird thoughts, anxiety, nightmares, and hallucinations, occur with parenteral doses above 60 mg. Epidemiological data suggest that overdose with pentazocine alone rarely causes death. High doses produce marked respiratory depression associated with increased blood pressure and tachycardia. The respiratory depression is antagonized by naloxone. Pentazocine is irritating when administered subcutaneously or intramuscularly. Repeated injections over long periods may cause extensive fibrosis of subcutaneous and muscular tissue. Patients who have been receiving opioids on a regular basis may experience abstinence signs and symptoms when given pentazocine. After an opioid-free interval of 1 to 2 days, it is usually possible to administer pentazocine without producing such withdrawal effects.

Tolerance and Physical Dependence. With frequent and repeated use, tolerance develops to the analgesic and subjective effects of pentazocine. However, pentazocine does not prevent or ameliorate the morphine withdrawal syndrome. Instead, when high doses of pentazocine are given to subjects dependent on morphine, it precipitates withdrawal symptoms because of its antagonistic actions at the μ receptor.

After long-term administration (60 mg every 4 hours), postaddicts develop physical dependence that can be demonstrated by abrupt withdrawal or by the administration of naloxone. The withdrawal syndrome after chronic doses of more than 500 mg per day, although milder in intensity than withdrawal from morphine, includes abdominal cramps, anxiety, chills, elevated temperature, vomiting, lacrimation, and sweating. Pentazocine withdrawal symptoms can be managed by gradual reduction of pentazocine itself or by substitution of μ-receptor agonists, such as morphine or methadone. A syndrome of withdrawal from pentazocine also has been observed in neonates.

Therapeutic Uses. Pentazocine is used as an analgesic. Although the risk of drug dependence exists, it may be lower than that associated with the use of morphine-like drugs in similar circumstances. Because abuse patterns appear to be less likely to develop with oral administration, this route should be used whenever possible.

Pentazocine lactate (TALWIN) is available as a solution for injection. In an effort to reduce the use of tablets as a source of injectable pentazocine, tablets for oral use now contain *pentazocine hydrochloride* (equivalent to 50 mg of the base) and *naloxone hydrochloride* (equivalent to 0.5 mg of the base; TALWIN NX). After oral ingestion, naloxone is destroyed rapidly by the liver; however, if the material is dissolved and injected, the naloxone produces aversive effects in subjects dependent on opioids. Tablets containing mixtures of pentazocine with aspirin (TALWIN COMPOUND) or acetaminophen (TALCEN) also are available. In terms of analgesic effect, 30 to 60 mg of pentazocine given parenterally is approximately equivalent to 10 mg of morphine. An oral dose of about 50 mg of pentazocine results in analgesia equivalent to that produced by 60 mg of codeine orally.

Nalbuphine

Nalbuphine is related structurally to both naloxone and oxymorphone (*see* Table 23–5). It is an agonist/antagonist opioid with a spectrum of effects that qualitatively resembles that of pentazocine; however, nalbuphine is a more potent antagonist at μ receptors and is less likely to produce dysphoric side effects than is pentazocine.

Pharmacological Actions and Side Effects. An intramuscular dose of 10 mg of nalbuphine is equianalgesic to 10 mg of morphine, with similar onset and duration of both analgesic and subjective effects. Nalbuphine depresses respiration as much as do equianalgesic doses of morphine. However, nalbuphine exhibits a ceiling effect, such that increases in dosage beyond 30 mg produce no further respiratory depression. However, a ceiling effect for analgesia also is reached at this point. In contrast to pentazocine and butorphanol, 10 mg of nalbuphine given to patients with stable coronary artery disease does not produce an increase in cardiac index, pulmonary arterial pressure, or cardiac work, and systemic blood pressure is not significantly altered; these indices also are relatively stable when nalbuphine is given to patients with acute myocardial infarction (*see* Roth *et al.*, 1988). Its gastrointestinal effects are probably similar to those of pentazocine. Nalbuphine produces few side effects at doses of 10 mg or less; sedation, sweating, and headache are the most common. At much higher doses (70 mg), psychotomimetic side effects (dysphoria, racing thoughts, and distortions of body image) can occur. Nalbuphine is metabolized in the liver and has a half-life in plasma of 2 to 3 hours. Given orally, nalbuphine is 20% to 25% as potent as when given intramuscularly.

Tolerance and Physical Dependence. In subjects dependent on low doses of morphine (60 mg per day), nalbuphine precipitates an abstinence syndrome. Prolonged administration of nalbuphine can produce physical dependence. The withdrawal syndrome is similar in intensity to that seen with pentazocine. The potential for abuse of parenteral nalbuphine in subjects not dependent on μ-receptor agonists is probably similar to that of parenteral pentazocine.

Therapeutic Uses. *Nalbuphine hydrochloride* (NUBAIN) is used to produce analgesia. Because it is an agonist/antagonist, administration to patients who have been receiving morphine-like opioids may create difficulties unless a brief drug-free interval is interposed. The usual adult dose is 10 mg parenterally every 3 to 6 hours; this may be increased to 20 mg in nontolerant individuals.

Butorphanol

Butorphanol is a morphinan congener with a profile of actions similar to those of pentazocine. The structural formula of butorphanol is shown in Table 23–5.

Pharmacological Actions and Side Effects. In postoperative patients, a parenteral dose of 2 to 3 mg of butorphanol produces analgesia and respiratory depression approximately equal to that produced by 10 mg of morphine or 80 to 100 mg of meperidine; the onset, peak, and duration of action are similar to those that follow the administration of morphine. The plasma half-life of butorphanol is about 3 hours. Like pentazocine, analgesic doses of butorphanol produce an increase in pulmonary arterial pressure and in the work of the heart; systemic arterial pressure is slightly decreased (Popio *et al.*, 1978).

The major side effects of butorphanol are drowsiness, weakness, sweating, feelings of floating, and nausea. While the incidence of psychotomimetic side effects is lower than that with equianalgesic doses of pentazocine, they are qualitatively similar. Physical dependence on butorphanol can occur.

Therapeutic Uses. *Butorphanol tartrate* (STADOL) is better suited for the relief of acute rather than chronic pain. Because of its side effects on the heart, it is less useful than morphine or meperidine in patients with congestive heart failure or myocardial infarction. The usual dose is between 1 and 4 mg of the tartrate given intramuscularly, or 0.5 to 2 mg given intravenously every 3 to 4 hours. A nasal formulation (STADOL NS) is available and has proven to be effective. This formulation is particularly useful for patients with severe headaches who may be unresponsive to other forms of treatment.

Buprenorphine

Buprenorphine is a semisynthetic, highly lipophilic opioid derived from thebaine (*see* Table 23–5). It is 25 to 50 times more potent than morphine.

Pharmacological Actions and Side Effects. Buprenorphine produces analgesia and other CNS effects that are qualitatively similar to those of morphine. About 0.4 mg of buprenorphine is equianalgesic with 10 mg of morphine given intramuscularly (Wallenstein *et al.*, 1986). Although variable, the duration of analgesia is usually longer than that of morphine. Some of the subjective and respiratory-depressant effects are unequivocally slower in onset and longer lasting than those of morphine. For example, peak miosis occurs about 6 hours after intramuscular injection, while maximal respiratory depression is observed at about 3 hours.

Buprenorphine appears to be a partial μ-receptor agonist. Depending on the dose, buprenorphine may cause symptoms of abstinence in patients who have been receiving μ-receptor agonists (morphine-like drugs) for several weeks. It antagonizes the respiratory depression produced by anesthetic doses of fentanyl about as well as does naloxone, without completely preventing opioid pain relief (Boysen *et al.*, 1988). Although respiratory depression has not been a major problem in clinical trials, it is not clear whether or not there is a ceiling for this effect (as seen with nalbuphine and pentazocine). The respiratory depression and other effects of buprenorphine can be prevented by prior administration of naloxone, but they are not readily reversed by high doses of naloxone once the effects have been produced. This suggests that buprenorphine dissociates very slowly from opioid receptors. The half-life for dissociation from the μ receptor is 166 minutes for buprenorphine, as opposed to 7 minutes for fentanyl (Boas and Villiger, 1985). Therefore, plasma levels of buprenorphine may not parallel clinical effects. Cardiovascular and other side effects (sedation, nausea, vomiting, dizziness, sweating, and headache) appear to be similar to those of morphine-like opioids.

Buprenorphine is relatively well absorbed by most routes. Administered sublingually, the drug (0.4 to 0.8 mg) produces satisfactory analgesia in postoperative patients. Concentrations

in blood peak within 5 minutes after intramuscular injection and within 1 to 2 hours after oral or sublingual administration. While the half-life in plasma has been reported to be about 3 hours, this value bears little relationship to the rate of disappearance of effects (*see* above). Both *N*-dealkylated and conjugated metabolites are detected in the urine, but most of the drug is excreted unchanged in the feces. About 96% of the circulating drug is bound to protein.

Physical Dependence. When buprenorphine is discontinued, a withdrawal syndrome develops that is delayed in onset for 2 days to 2 weeks; this consists of typical, but generally not very severe, morphine-like withdrawal signs and symptoms, and it persists for about 1 to 2 weeks (Bickel *et al.*, 1988; Fudala *et al.*, 1989).

Therapeutic Uses. *Buprenorphine.* (BUPRENEX) may be used as an analgesic and also has proven to be useful as a maintenance drug for opioid-dependent subjects (Johnson *et al.*, 2000). The drug was approved provisionally for use in the treatment of heroin addiction when the Drug Addiction Treatment Act was passed by the United States Congress and signed by the President in October of 2000. Approval by the Food and Drug Administration is pending.

The usual intramuscular or intravenous dose for analgesia is 0.3 mg, given every 6 hours. Sublingual doses of 0.4 to 0.8 mg produce effective analgesia, and doses of 6 to 8 mg appear to be about equal to 60 mg of methadone as a maintenance agent.

Other Agonist/Antagonists

Meptazinol is an agonist/antagonist opioid that is about one-tenth as potent as morphine in producing analgesia. Its duration of action is somewhat shorter than that of morphine. Meptazinol also has cholinergic actions that may contribute to its analgesic effects (*see* Holmes and Ward, 1985). Nevertheless, its analgesic actions are antagonized by naloxone, and it can precipitate withdrawal in animals dependent on μ-receptor agonists. The potential for abuse of meptazinol is less than that of morphine because dysphoric side effects appear when the dose is increased. *Dezocine* (DALGAN), an aminotetralin, is another agonist/antagonist; its potency and duration of analgesic effect are similar to those of morphine. Increasing the dose above 30 mg does not produce progressively more severe respiratory depression. In postaddicts, its subjective effects are similar to those of μ-agonist opioids (Jasinski and Preston, 1985).

OPIOID ANTAGONISTS

Under ordinary circumstances, the drugs to be discussed in this section produce few effects unless opioids with agonistic actions have been administered previously. However, when the endogenous opioid systems are activated, as in shock or certain forms of stress, the administration of an opioid antagonist alone may have visible consequences. These agents have obvious therapeutic utility in the treatment of overdosage with opioids. As the understanding of the role of endogenous opioid systems in pathophysiological states increases, additional therapeutic indications for these antagonists may develop.

Chemistry. Relatively minor changes in the structure of an opioid can convert a drug that is primarily an agonist into one with antagonistic actions at one or more types of opioid receptors. The most common such substitution is that of a larger moiety (*e.g.*, an allyl or methylcyclopropyl group) for the *N*-methyl group that is typical of the μ-receptor agonists. Such substitutions transform morphine to *nalorphine, levorphanol* to *levallorphan,* and oxymorphone to *naloxone* or *naltrexone* (*see* Table 23–5). In some cases, congeners are produced that are competitive antagonists at μ receptors but that also have agonistic actions at κ receptors. Nalorphine and levallorphan have such properties. Other congeners, especially naloxone and naltrexone, appear to be devoid of agonistic actions and probably interact with all types of opioid receptors, albeit with widely different affinities (*see* Martin, 1983).

Nalmefene (REVIX) is a relatively pure μ-receptor antagonist that is more potent than naloxone (Dixon *et al.*, 1986). A number of other nonpeptide antagonists have been developed that are relatively selective for individual types of opioid receptors. These include *cypridime* and *β-funaltrexamine* (β-FNA) (μ), *naltrindole* (δ), and *nor-binaltorphimine* (κ) (*see* Portoghese, 1989; Pasternak, 1993).

Pharmacological Properties

If endogenous opioid systems have not been activated, the pharmacological actions of opioid antagonists depend on whether or not an opioid agonist has been administered previously, on the pharmacological profile of that opioid, and on the degree to which physical dependence on an opioid has developed.

Effects in the Absence of Opioid Drugs. Subcutaneous doses of naloxone (NARCAN; up to 12 mg) produce no discernible subjective effects in human beings, and 24 mg causes only slight drowsiness. Naltrexone (REVIA) also appears to be a relatively pure antagonist but with higher oral efficacy and a longer duration of action. At high doses, both naloxone and naltrexone may have some special agonistic effects. However, these are of little clinical significance. At doses in excess of 0.3 mg/kg of naloxone, normal subjects show increased systolic blood pressure and decreased performance on tests of memory. High doses of naltrexone appeared to cause mild dysphoria in one study but almost no subjective effect in several others (*see* Gonzalez and Brogden, 1988).

Although high doses of antagonists might be expected to alter the actions of endogenous opioid peptides, the detectable effects are usually both subtle and limited (Cannon and Liebeskind, 1987). Most likely, this reflects the low levels of tonic activity of the opioid systems. In this regard, analgesic

effects can be differentiated from endocrine effects, in which naloxone causes readily demonstrable changes in hormone levels (*see* below). It is interesting that naloxone appears to block the analgesic effects of placebo medications and acupuncture. In laboratory animals, the administration of naloxone will reverse or attenuate the hypotension associated with shock of diverse origins including that caused by anaphylaxis, endotoxin, hypovolemia, and injury to the spinal cord; opioid agonists aggravate these conditions (Amir, 1988). Naloxone apparently acts to antagonize the actions of endogenous opioids that are mobilized by pain or stress and that are involved in the regulation of blood pressure by the CNS. Although neural damage that follows trauma to the spinal cord or cerebral ischemia also appears to involve endogenous opioids, it is not certain whether opioid antagonists can prevent damage to these or other organs and/or increase rates of survival. Nevertheless, opioid antagonists can reduce the extent of injury in some animal models, perhaps by blocking κ receptors (Faden, 1988).

As noted above, endogenous opioid peptides participate in the regulation of pituitary secretion, apparently by exerting tonic inhibitory effects on the release of certain hypothalamic hormones (*see* Chapter 56). Thus, the administration of naloxone or naltrexone increases the secretion of gonadotropin-releasing hormone and corticotropin-releasing factor and elevates the plasma concentrations of LH, FSH, and ACTH, as well as the hormones produced by their target organs. Antagonists do not consistently alter basal or stress-induced concentrations of prolactin in plasma in men; paradoxically, naloxone *stimulates* the release of prolactin in women. Opioid antagonists augment the increases in plasma concentrations of cortisol and catecholamines that normally accompany stress or exercise. The neuroendocrine effects of opioid antagonists have been reviewed (Howlett and Rees, 1986). Endogenous opioid peptides probably have some role in the regulation of feeding or energy metabolism, because opioid antagonists increase energy expenditure and interrupt hibernation in appropriate species and induce weight loss in genetically obese rats. The antagonists also prevent stress-induced overeating and obesity in rats. These observations have led to the experimental use of opioid antagonists in the treatment of human obesity, especially that associated with stress-induced eating disorders. However, naltrexone does not accelerate weight loss in very obese subjects, even though short-term administration of opioid antagonists reduce food intake in both lean and obese individuals (Atkinson, 1987).

Antagonistic Actions. Small doses (0.4 to 0.8 mg) of naloxone given intramuscularly or intravenously prevent or promptly reverse the effects of μ-receptor agonists. In patients with respiratory depression, an increase in respiratory rate is seen within 1 or 2 minutes. Sedative effects are reversed, and blood pressure, if depressed, returns to normal. Higher doses of naloxone are required to antagonize the respiratory-depressant effects of buprenorphine; 1 mg of naloxone intravenously completely blocks the effects of 25 mg of heroin. Naloxone reverses the psychotomimetic and dysphoric effects of agonist/antagonist agents such as pentazocine, but much higher doses (10 to 15 mg) are required. The duration of antagonistic effects depends on the dose but is usually 1 to 4 hours. Antagonism of opioid effects by naloxone often is accompanied by "overshoot" phenomena. For example, respiratory rate depressed by opioids transiently becomes higher than that prior to the period of depression. Rebound release of catecholamines may cause hypertension, tachycardia, and ventricular arrhythmias. Pulmonary edema also has been reported after naloxone administration.

Effects in Physical Dependence. In subjects who are dependent on morphine-like opioids, small subcutaneous doses of naloxone (0.5 mg) precipitate a moderate-to-severe withdrawal syndrome that is very similar to that seen after abrupt withdrawal of opioids, except that the syndrome appears within minutes after administration and subsides in about 2 hours. The severity and duration of the syndrome are related to the dose of the antagonist and to the degree and type of dependence. Higher doses of naloxone will precipitate a withdrawal syndrome in patients dependent on pentazocine, butorphanol, or nalbuphine. Naloxone produces "overshoot" phenomena suggestive of early acute physical dependence 6 to 24 hours after a single dose of a μ agonist (*see* Heishman *et al.*, 1989).

Tolerance and Physical Dependence. Even after prolonged administration of high doses, discontinuation of naloxone is not followed by any recognizable withdrawal syndrome, and the withdrawal of naltrexone, another relatively pure antagonist, produces very few signs and symptoms. However, long-term administration of antagonists increases the density of opioid receptors in the brain and causes a temporary exaggeration of responses to the subsequent administration of opioid agonists (Yoburn *et al.*, 1988). Naltrexone and naloxone have little or no potential for abuse.

Absorption, Fate, and Excretion. Although absorbed readily from the gastrointestinal tract, naloxone is almost completely metabolized by the liver before reaching the systemic circulation and thus must be administered parenterally. The drug is absorbed rapidly from parenteral sites of injection and is metabolized in the liver, primarily by conjugation with glucuronic acid; other metabolites are produced in small amounts. The half-life of naloxone is about 1 hour, but its clinically effective duration of action can be even less.

Compared with naloxone, naltrexone retains much more of its efficacy by the oral route, and its duration of action approaches 24 hours after moderate oral doses.

Peak concentrations in plasma are reached within 1 to 2 hours and then decline with an apparent half-life of approximately 3 hours; this value does not change with long-term use. Naltrexone is metabolized to 6-naltrexol, which is a weaker antagonist but has a longer half-life of about 13 hours. Naltrexone is much more potent than naloxone, and 100-mg oral doses given to patients addicted to opioids produce concentrations in tissues sufficient to block the euphorigenic effects of 25-mg intravenous doses of heroin for 48 hours (*see* Gonzalez and Brogden, 1988).

Therapeutic Uses

Opioid antagonists have established uses in the treatment of opioid-induced toxicity, especially respiratory depression; in the diagnosis of physical dependence on opioids; and as therapeutic agents in the treatment of compulsive users of opioids, as discussed in Chapter 24. Their potential utility in the treatment of shock, stroke, spinal cord and brain trauma, and other disorders that may involve mobilization of endogenous opioid peptides remains to be established. *Naltrexone* is approved by the United States Food and Drug Administration for treatment of alcoholism (*see* Chapters 18 and 24).

Treatment of Opioid Overdosage. *Naloxone hydrochloride* is used to treat opioid overdose. As discussed earlier, it acts rapidly to reverse the respiratory depression associated with high doses of opioids. However, it should be used cautiously, since it also can precipitate withdrawal in dependent subjects and cause undesirable cardiovascular side effects. By carefully titrating the dose of naloxone, it usually is possible to antagonize the respiratory-depressant actions without eliciting a full withdrawal syndrome. The duration of action of naloxone is relatively short, and it often must be given repeatedly or by continuous infusion. Opioid antagonists also have been effectively employed to decrease neonatal respiratory depression secondary to the intravenous or intramuscular administration of opioids to the mother. In the neonate, the initial dose is 10 μg/kg, given intravenously, intramuscularly, or subcutaneously.

CENTRALLY ACTIVE ANTITUSSIVE AGENTS

Cough is a useful physiological mechanism that serves to clear the respiratory passages of foreign material and excess secretions. It should not be suppressed indiscriminately. There are, however, many situations in which cough does not serve any useful purpose but may, instead, only annoy the patient or prevent rest and sleep. Chronic cough can contribute to fatigue, especially in elderly patients. In such situations the physician should use a drug that will reduce the frequency or intensity of the coughing. The cough reflex is complex, involving the central and peripheral nervous systems as well as the smooth muscle of the bronchial tree. It has been suggested that irritation of the bronchial mucosa causes bronchoconstriction, which, in turn, stimulates cough receptors (which probably represent a specialized type of stretch receptor) located in tracheobronchial passages. Afferent conduction from these receptors is *via* fibers in the vagus nerve; central components of the reflex probably involve several mechanisms or centers that are distinct from the mechanisms involved in the regulation of respiration.

The drugs that directly or indirectly can affect this complex mechanism are diverse. For example, cough may be the first or only symptom in bronchial asthma or allergy, and in such cases bronchodilators (*e.g.*, β_2-adrenergic receptor agonists; *see* Chapter 10) have been shown to reduce cough without having any significant central effects; other drugs act primarily on the central or the peripheral nervous system components of the cough reflex. The early literature on antitussives has been reviewed by Eddy *et al.* (1969).

A number of drugs are known to reduce cough as a result of their central actions, although the exact mechanisms are still not entirely clear. Included among them are the opioid analgesics discussed above (codeine and hydrocodone are the opioids most commonly used to suppress cough), as well as a number of nonopioid agents. Cough suppression often occurs with lower doses of opioids than those needed for analgesia. A 10- or 20-mg oral dose of codeine, although ineffective for analgesia, produces a demonstrable antitussive effect, and higher doses produce even more suppression of chronic cough.

In selecting a specific centrally active agent for a particular patient, the significant considerations are its antitussive efficacy against pathological cough and the incidence and type of side effects to be expected. In the majority of situations requiring a cough suppressant, liability for abuse need not be a major consideration. Most of the nonopioid agents now offered as antitussives are effective against cough induced by a variety of experimental techniques. However, the ability of these tests to predict clinical efficacy is limited.

Dextromethorphan. *Dextromethorphan* (*d*-3-methoxy-*N*-methylmorphinan) is the *d* isomer of the codeine analog methorphan; however, unlike the *l* isomer, it has no

analgesic or addictive properties and does not act through opioid receptors. The drug acts centrally to elevate the threshold for coughing. Its effectiveness in patients with pathological cough has been demonstrated in controlled studies; its potency is nearly equal to that of codeine. Compared with codeine, dextromethorphan produces fewer subjective and gastrointestinal side effects (Matthys *et al.*, 1983). In therapeutic dosages, the drug does not inhibit ciliary activity, and its antitussive effects persist for 5 to 6 hours. Its toxicity is low, but extremely high doses may produce CNS depression.

Sites that bind dextromethorphan with high affinity have been identified in membranes from various regions of the brain (Craviso and Musacchio, 1983). Although dextromethorphan is known to function as an NMDA-receptor antagonist, these binding sites are not limited to the known distribution of NMDA receptors (Elliott *et al.*, 1994). Thus, the mechanism by which dextromethorphan exerts its antitussive effects is still unclear. Two other known antitussives, carbetapentane and caramiphen, also bind avidly to this site, but codeine, levopropoxyphene, and other antitussive opioids (as well as naloxone) are not bound. Although noscapine (*see* below) enhances the affinity of dextromethorphan, it appears to interact with distinct binding sites (Karlsson *et al.*, 1988). The relationship of these binding sites to antitussive actions is not known; however, these observations, coupled with the ability of naloxone to antagonize the antitussive effects of codeine but not those of dextromethorphan, indicate that cough suppression can be achieved by a number of different mechanisms. The average adult dosage of *dextromethorphan hydrobromide* is 10 to 30 mg three to six times daily; however, as is the case with codeine, higher doses often are required. The drug is generally marketed for "over-the-counter" sale in numerous syrups and lozenges or in combinations with antihistamines and other agents.

Other Drugs. *Levopropoxyphene napsylate,* the *l*-isomer of dextropropoxyphene, in doses of 50 to 100 mg orally, appears to suppress cough to about the same degree as does 30 mg of dextromethorphan. Unlike dextropropoxyphene, levopropoxyphene has little or no analgesic activity.

Noscapine is a naturally occurring opium alkaloid of the benzylisoquinoline group; except for its antitussive effect, it has no significant actions on the CNS in doses within the therapeutic range. The drug is a potent releaser of histamine, and large doses cause bronchoconstriction and transient hypotension.

Other drugs that have been used as centrally acting antitussives include *carbetapentane, caramiphen, chlophedianol, diphenhydramine,* and *glaucine.* Each is a member of a distinct pharmacological class unrelated to the opioids. The mechanism of action of diphenhydramine, an antihistamine, is unclear. Although sedative effects are common, paradoxical excitement may be seen in infants; dryness of mucous membranes caused by anticholinergic effects and thickening of mucus may be a disadvantage. In general, the toxicity of these agents is low, but controlled clinical studies are still insufficient to determine whether or not they merit consideration as alternatives to more thoroughly studied agents.

Pholcodine [3-*O*-(2-morpholinoethyl)morphine] is used clinically in many countries outside the United States. Although structurally related to the opioids, it has no opioid-like actions because the substitution at the 3-position is not removed by metabolism. Pholcodine is at least as effective as codeine as an antitussive; it has a long half-life and can be given once or twice daily (*see* Findlay, 1988).

Benzonatate (TESSALON) is a long-chain polyglycol derivative chemically related to procaine and believed to exert its antitussive action on stretch or cough receptors in the lung, as well as by a central mechanism. It has been administered by all routes; the oral dosage is 100 mg three times daily, but higher doses have been used.

THERAPEUTIC USES OF OPIOID ANALGESICS

Sir William Osler called morphine "God's own medicine." Opioids are still the mainstay of pain treatment. However, the development of new analgesic compounds and new routes of administration have increased the therapeutic options available to clinicians, while at the same time helping to minimize undesirable side effects. In this section, we will outline guidelines for rational drug selection, discuss routes of administration other than the standard oral and parenteral methods, and outline general principles for the use of opioids in acute and chronic pain states.

Extensive efforts by many individuals and organizations have resulted in the publication of many useful guidelines for the administration of opioids. These have been developed for a number of clinical situations, including acute pain, trauma, cancer, nonmalignant chronic pain, and treatment of pain in children (Agency for Health Care Policy and Research, 1992a, 1992b, 1994; International Association for the Study of Pain, 1992; American Pain Society, 1999; Grossman *et al.*, 1999; World Health Organization, 1998; Berde *et al.*, 1990). These guidelines provide comprehensive discussions of dosing regimens and drug selection and also provide protocols for the management of complex conditions. In the case of cancer pain, adherence to standardized protocols for cancer pain management (Agency for Health Care Policy and Research, 1994) has been shown to improve pain management significantly (Du Pen *et al.*, 1999). Guidelines for the oral and parenteral dosing of commonly used opioids are presented in Table 23–6.

These guidelines are for acute pain management in opioid-naïve patients. Adjustments will need to be made for use in opioid-tolerant patients and in chronic pain states. For children under 6 months of age, especially those who are ill or premature, expert consultation should be obtained. The pharmacokinetics and potency of opioids

Table 23–6
Dosing Data for Opioid Analgesics

DRUG	APPROXIMATE EQUIANALGESIC ORAL DOSE	APPROXIMATE EQUIANALGESIC PARENTERAL DOSE	RECOMMENDED STARTING DOSE (ADULTS MORE THAN 50 kg BODY WEIGHT)		RECOMMENDED STARTING DOSE (CHILDREN AND ADULTS LESS THAN 50 kg BODY WEIGHT)[1]	
			ORAL	PARENTERAL	ORAL	PARENTERAL
Opioid Agonist						
Morphine[2]	30 mg q 3–4 hr (around-the-clock dosing) 60 mg q 3–4 hr (single dose or intermittent dosing)	10 mg q 3–4 hr	30 mg q 3–4 hr	10 mg q 3–4 hr	0.3 mg/kg q 3–4 hr	0.1 mg/kg q 3–4 hr
Codeine[3]	130 mg q 3–4 hr	75 mg q 3–4 hr	60 mg q 3–4 hr	60 mg q 2 hr (intramuscular/ subcutaneous)	1 mg/kg q 3–4 hr[4]	Not recommended
Hydromophone[2] (DILAUDID)	7.5 mg q 3–4 hr	1.5 mg q 3–4 hr	6 mg q 3–4 hr	1.5 mg q 3–4 hr	0.06 mg/kg q 3–4 hr	0.015 mg/kg q 3–4 hr
Hydrocodone (in LORCET, LORTAB, VICODIN, others)	30 mg q 3–4 hr	Not available	10 mg q 3–4 hr	Not available	0.2 mg/kg q 3–4 hr[4]	Not available
Levorphanol (LEVO-DROMORAN)	4 mg q 6–8 hr	2 mg q 6–8 hr	4 mg q 6–8 hr	2 mg q 6–8 hr	0.04 mg/kg q 6–8 hr	0.02 mg/kg q 6–8 hr
Meperidine (DEMEROL)	300 mg q 2–3 hr	100 mg q 3 hr	Not recommended	100 mg q 3 hr	Not recommended	0.75 mg/kg q 2–3 hr
Methadone (DOLOPHINE, others)	20 mg q 6–8 hr	10 mg q 6–8 hr	20 mg q 6–8 hr	10 mg q 6–8 hr	0.2 mg/kg q 6–8 hr	0.1 mg/kg q 6–8 hr
Oxycodone (ROXICODONE, also in PERCOCET, PERCODAN, TYLOX, others)[7]	30 mg q 3–4 hr	Not available	10 mg q 3–4 hr	Not available	0.2 mg/kg q 3–4 hr[4]	Not available
Oxymorphone[2] (NUMORPHAN)	Not available	1 mg q 3–4 hr	Not available	1 mg q 3–4 hr	Not recommended	Not recommended
Propoxyphene (DARVON)	130 mg[5]	Not available	65 mg q 4–6 hr[5]	Not available	Not recommended	Not recommended
Tramadol[6] (ULTRAM)	100 mg[5]	100 mg	50–100 mg q 6 hr[5]	50–100 mg q 6 hr[5]	Not recommended	Not recommended
Opioid Agonist-Antagonist or Partial Agonist						
Buprenorphine (BUPRENEX)	Not available	0.3–0.4 mg q 6–8 hr	Not available	0.4 mg q 6–8 hr	Not available	0.004 mg/kg q 6–8 hr
Butorphanol (STADOL)	Not available	2 mg q 3–4 hr	Not available	2 mg q 3–4 hr	Not available	Not recommended
Nalbuphine (NUBAIN)	Not available	10 mg q 3–4 hr	Not available	10 mg q 3–4 hr	Not available	0.1 mg/kg q 3–4 hr
Pentazocine (TALWIN, others)	150 mg q 3–4 hr	60 mg q 3–4 hr	50 mg q 4–6 hr	Not recommended	Not recommended	Not recommended

NOTE: Published tables vary in the suggested doses that are equianalgesic to morphine. Clinical response is the criterion that must be applied for each patient; titration to clinical response is necessary. Because there is not complete cross tolerance among these drugs, it is usually necessary to use a lower than equianalgesic dose when changing drugs and to retitrate to response.

Caution: Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting drug metabolism and kinetics.

[1] *Caution:* Doses listed for patients with body weight less than 50 kg cannot be used as initial starting doses in babies less than 6 months of age. Consult the *Clinical Practice Guideline for Acute Pain Management: Operative or Medical Procedures and Trauma* section on management of pain in neonates for recommendations.

[2] For morphine, hydromorphone, and oxymorphone, rectal administration is an alternate route for patients unable to take oral medications, but equianalgesic doses may differ from oral and parenteral doses because of pharmacokinetic differences.

[3] *Caution:* Codeine doses above 65 mg often are not appropriate due to diminishing incremental analgesia with increasing doses but continually increasing constipation and other side effects.

[4] *Caution:* Doses of aspirin and acetaminophen in combination opioid/NSAID preparations must also be adjusted to the patient's body weight. Maximum acetaminophen dose: 4 g/day in adults, 90 mg/kg per day in children.

[5] Doses for moderate pain not necessarily equivalent to 30 mg oral or 10 mg parenteral morphine.

[6] Risk of seizures: parenteral formulation not available in the U.S.

[7] OXYCONTIN is an extended-release preparation containing up to 160 mg of oxycodone per tablet and recommended for use every 12 hours. It has been subject to substantial abuse.

ABBREVIATION: q, every.

SOURCE: Modified from Agency for Healthcare Policy and Research, 1992a, with permission.

can be substantially altered in these patients, and in some cases there is a significant risk of apnea. It also should be noted that there is substantial individual variability in responses to opioids. A standard intramuscular dose of 10 mg of morphine sulfate will relieve severe pain adequately in only 2 of 3 patients. Adjustments will have to be made based on clinical response.

In general, it is recommended that opioids always be combined with other analgesic agents, such as nonsteroidal anti-inflammatory drugs (NSAIDS) or acetaminophen. In this way, one can take advantage of additive analgesic effects and minimize the dose of opioids and thus undesirable side effects. In some situations, NSAIDS can provide analgesia equal to that produced by 60 mg of codeine. Potentiation of opioid action by NSAIDs may be due to increased conversion of arachidonic acid to 12-lipoxygenase products that facilitate effects of opioids on K^+ channels (Vaughan *et al.*, 1997). This "opioid-sparing" strategy is the backbone of the "analgesic ladder" for pain management proposed by the World Health Organization (1990). Weaker opioids can be supplanted by stronger opioids in cases of moderate and severe pain. In addition, analgesics always should be dosed in a continuous or "around the clock" fashion rather than on an as needed basis for chronic severe pain. This provides more consistent analgesic levels and avoids unnecessary suffering. Knowledge of the pharmacological profiles of analgesics allows the rational selection of dosing intervals without risk of overdosage.

Factors guiding the selection of specific opioid compounds for pain treatment include potency, pharmacokinetic characteristics, and the routes of administration available. A more potent compound could be useful when high doses of opioid are required, so the medicine can be given in a smaller volume. Duration of action also is an important consideration. For example, a long-acting opioid such as methadone may be appropriate when less-frequent dosing is desired. For short, painful procedures, a quick-acting, fast-dissipating compound such as remifentanil would be a useful choice. In special cases, where a lower addiction risk is required or in patients unable to tolerate other opioids, a partial agonist or mixed agonist/antagonist compound might be a rational choice. The properties of some commonly used orally-administered opioids are discussed in more detail below.

Morphine is available for oral use in standard and controlled-release preparations. Due to first-pass metabolism, morphine is two- to sixfold less potent orally than parenterally. This is important to remember when converting a patient from parenteral to oral medication. There is wide variability in the first-pass metabolism, and the dose should be titrated to the patient's needs. In children who weigh less than 50 kg, morphine can be given at 0.1 mg/kg every 3 to 4 hours parenterally or at 0.3 mg/kg orally.

Codeine is widely used only due to its high oral/parenteral potency ratio. Orally, codeine at 30 mg is approximately equianalgesic to 325 to 600 mg of aspirin. Combinations of codeine with aspirin or acetaminophen usually provide additive actions, and at these doses analgesic efficacy can exceed that of 60 mg of codeine (*see* Beaver, 1988). Many drugs can be used instead of either morphine or codeine, as shown in Table 23–6. Oxycodone, with its high oral/parenteral potency ratio, is widely used in combination with aspirin (PERCODAN, others) or acetaminophen (PERCOCET 2.5/325, others), although it is available alone (ROXICODINE, others).

Heroin (diacetylmorphine) is not available for therapeutic use in the United States, although it has been used in the United Kingdom. Given intramuscularly, it is approximately twice as potent as morphine. Pharmacologically, heroin is very similar to morphine and does not appear to have any unique therapeutic advantages over the available opioids (Sawynok, 1986; Kaiko *et al.*, 1981). It also may be helpful to employ other agents (adjuvants) that enhance opioid analgesia and that may add beneficial effects of their own. For example, the combination of an opioid with a small dose of amphetamine may augment analgesia while reducing the sedative effects. Certain antidepressants, such as amitriptyline and desipramine, also may enhance opioid analgesia, and they may have analgesic actions in some types of neuropathic (deafferentation) pain (*see* McQuay, 1988). Other potentially useful adjuvants include certain antihistamines, anticonvulsants such as carbamazepine and phenytoin, and glucocorticoids.

Alternative Routes of Administration

In addition to the traditional oral and parenteral formulations for opioids, many other methods have been developed in an effort to improve therapeutic efficacy while minimizing side effects. These routes also improve the ease of use of opioids, and increase patient satisfaction.

Patient-Controlled Analgesia (PCA). With this modality, the patient has limited control of the dosing of opioid from an infusion pump within tightly mandated parameters. PCA can be used for intravenous or epidural infusion. This technique avoids any delays in administration and permits greater dosing flexibility than other regimens, better adapting to individual differences in responsiveness to pain and to opioids. It also gives the patient a greater sense of control. With shorter-acting opioids, serious toxicity or excessive use rarely occurs. An early concern that self-administration of opioids would increase the probability of addiction has not materialized. PCA is suitable for both adults and children, and it is preferred over intramuscular injections for postoperative pain control (Rodgers *et al.*, 1988).

Computer-Assisted Continuous Infusion (CACI). The idea behind this mode of administration is to enable clinicians to

Table 23–7
Intraspinal Opioids for the Treatment of Acute Pain

DRUG	SINGLE DOSE* (mg)	INFUSION RATE** (mg/hr)	ONSET (minutes)	DURATION OF EFFECT OF A SINGLE DOSE*** (hours)
Epidural				
Morphine	1–6	0.1–1.0	30	6–24
Meperidine	20–150	5–20	5	4–8
Methadone	1–10	0.3–0.5	10	6–10
Hydromorphone	1–2	0.1–0.2	15	10–16
Fentanyl	0.025–0.1	0.025–0.10	5	2–4
Sufentanil	0.01–0.06	0.01–0.05	5	2–4
Alfentanil	0.5–1	0.2	15	1–3
Subarachnoid				
Morphine	0.1–0.3		15	8–24+
Meperidine	10–30		?	10–24+
Fentanyl	0.005–0.025		5	3–6

*Low doses may be effective when administered to the elderly or when injected in the cervical or thoracic region.

**If combining with a local anesthetic, consider using 0.0625% bupivacaine.

***Duration of analgesia varies widely; higher doses produce longer duration.

SOURCE: Adapted from International Association for the Study of Pain, 1992.

titrate intravenous agents in a fashion similar to that used in delivering volatile agents (Sanford and Gutstein, 1995). CACI based on detailed pharmacokinetic models has been used successfully to administer opioids (Shafer *et al.*, 1990; Bailey *et al.*, 1993). However, true "closed-loop" control of opioid administration requires the capability of continuously measuring plasma opioid levels with indwelling sensors. Until such real-time measurement is available, accurate assessment of dose-effect relationships in patients is not possible.

Intraspinal Infusion. Administration of opioids into the epidural or intrathecal space provides more direct access to the first pain-processing synapse in the dorsal horn of the spinal cord. This permits the use of doses substantially lower than those required for oral or parenteral administration (*see* Table 23–7). Systemic side effects are thus decreased. However, epidural opioids have their own dose-dependent side effects, such as itching, nausea, vomiting, respiratory depression, and urinary retention. The use of hydrophilic opioids such as preservative-free morphine (DURAMORPH, others) permits more rostral spread of the compound, allowing it to directly affect supraspinal sites. As a consequence, after intraspinal morphine, delayed respiratory depression can be observed for as long as 24 hours after a bolus dose. While the risk of delayed respiratory depression is reduced with more lipophilic opioids, it is not eliminated. Extreme vigilance and appropriate monitoring are required for all patients receiving intraspinal narcotics. Nausea and vomiting also are more prominent symptoms with intraspinal morphine. However, supraspinal analgesic centers also can be stimulated, possibly leading to synergistic analgesic effects.

Analogous to the relationship between systemic opioids and NSAIDS, intraspinal narcotics often are combined with local anesthetics. This permits the use of lower concentrations of both agents, minimizing local anesthetic-induced complications of motor blockade and the opioid-induced complications listed above. Epidural administration of opioids has become popular in the management of postoperative pain and for providing analgesia during labor and delivery. Lower systemic opioid levels are achieved with epidural opioids, leading to less placental transfer and less potential for respiratory depression of the newborn (Shnider and Levinson, 1987). Intrathecal ("spinal" anesthesia) administration of opioids as a single bolus also is popular for acute pain management. Chronic intrathecal infusions generally are reserved for use in chronic pain patients.

Peripheral Analgesia. As previously mentioned, opioid receptors on peripheral nerves have been shown to respond to locally applied opioids during inflammation (Stein, 1995). Peripheral analgesia permits the use of lower doses, applied locally, than those necessary to achieve a systemic effect. The effectiveness

of this technique has been demonstrated in studies of postoperative pain (Stein *et al.*, 1991). These studies also suggest that peripherally acting opioid compounds would be effective in other selected circumstances without entering the CNS to cause many undesirable side effects. Development of such compounds and expansion of clinical applications of this technique currently are active areas of research.

Rectal Administration. This route is an alternative for patients with difficulty swallowing or other oral pathology and who prefer a less-invasive route than parenteral (De Conno *et al.*, 1995). This route is not well tolerated in most children. Onset of action is seen within 10 minutes. In the United States, morphine, hydromorphone, and oxymorphone are available in rectal suppository formulation (American Pain Society, 1999).

Administration by Inhalation. Preliminary studies have shown that opioids delivered by nebulizer can be an effective means of analgesic drug delivery (Worsley *et al.*, 1990; Higgins *et al.*, 1991). However, constant supervision is required when administering the drug, and variable delivery to the lungs can cause differences in therapeutic effect. In addition, possible environmental contamination is a concern. However, development of the inhaled route could provide a more convenient and cost-effective, adjunctive method of analgesic delivery for patients experiencing chronic pain.

Oral Transmucosal Administration. Opioids can be absorbed through the oral mucosa more rapidly than through the stomach. Bioavailability is greater due to avoidance of first pass metabolism, and lipophilic opioids are better absorbed by this route than are hydrophilic compounds such as morphine (Weinberg *et al.*, 1988). A transmucosal delivery system that suspends fentanyl in a dissolvable matrix has been approved for clinical use (ACTIQ). Its primary indication is for treatment of breakthrough cancer pain (Asburn *et al.*, 1989). In this setting, transmucosal fentanyl relieves pain within 15 minutes, and patients easily can titrate the appropriate dose. Transmucosal fentanyl also has been studied as a premedicant for children. However, this technique has been largely abandoned due to a substantial incidence of undesirable side effects such as respiratory depression, sedation, nausea, vomiting, and pruritus.

Transdermal or Iontophoretic Administration. Transdermal fentanyl patches are approved for use with sustained pain. The opioid permeates the skin, and a "depot" is established in the stratum corneum layer. Unlike other transdermal systems (*i.e.*, transdermal scopolamine), anatomic position of the patch does not affect absorption. However, fever and external heat sources of heat (heating pads, hot baths) can increase absorption of fentanyl and potentially lead to an overdose (Rose *et al.*, 1993). This modality is well suited for cancer pain treatment because of its ease of use, prolonged duration of action, and stable blood levels (Portenoy *et al.*, 1993). It may take up to 12 hours to develop analgesia and up to 16 hours to observe full clinical effect. Plasma levels stabilize after two sequential patch applications, and these kinetics do not appear to change with repeated applications (Portenoy, 1993). However, there may be a great deal of variability in plasma levels after a given dose. The plasma half-life after patch removal is about 17 hours. Thus, if excessive sedation or respiratory depression is experienced, antagonist infusions may need to be maintained for an extended period (Payne, 1992). Dermatological side effects from the patches, such as rash and itching, usually are mild.

Iontophoresis is the transport of soluble ions through the skin by using a mild electric current. This technique has been employed with morphine (Ashburn *et al.*, 1992). Fentanyl and sufentanil have been chemically modified and applied by iontophoresis in rats (Thysman and Preat, 1993). Effective analgesia was achieved in less than 1 hour, suggesting that iontophoresis could be a promising modality for postoperative pain. It should be noted that increasing the applied current will increase drug delivery and could lead to overdose. However, unlike transdermal opioids, a drug reservoir does not build up in the skin, thus limiting the duration of both main and side effects.

General Principles of Opioid Use

Opioid analgesics provide symptomatic relief of pain, but the underlying disease remains. The physician must weigh the benefits of this relief against any potential risk to the patient, which may be quite different in an acute compared with a chronic disease.

In acute problems, opioids will reduce the intensity of pain. However, physical signs (such as abdominal rigidity) will generally remain. Relief of pain also can facilitate history taking, examination, and the patient's ability to tolerate diagnostic procedures. Patients should not be evaluated inadequately because of the physician's unwillingness to prescribe analgesics, nor in most cases should analgesics be withheld for fear of obscuring the progression of underlying disease.

The problems that arise in the relief of pain associated with chronic conditions are more complex. Repeated daily administration eventually will produce tolerance and some degree of physical dependence. The degree will depend on the particular drug, the frequency of administration, and the quantity administered. The decision to control any chronic symptom, especially pain, by the repeated administration of an opioid must be made carefully. When pain is due to chronic, nonmalignant disease, measures other than opioid drugs should be employed to relieve chronic pain if they are effective and available. Such measures include the use of nonsteroidal antiinflammatory agents, local nerve block, antidepressant drugs, electrical stimulation, acupuncture, hypnosis, or behavioral modification (*see* Foley, 1985). However, highly selected subpopulations of chronic nonmalignant pain patients can be adequately maintained on opioids for extended periods of time (Portenoy, 1990).

In the usual doses, morphine-like drugs relieve suffering by altering the emotional component of the painful

experience as well as by producing analgesia. Control of pain, especially chronic pain, must include attention to both psychological factors and the social impact of the illness that sometimes play dominant roles in determining the suffering experienced by the patient. In addition to emotional support, the physician also must consider the substantial variability in both the patient's capacity to tolerate pain and the response to opioids. As a result, some patients may require considerably more than the average dose of a drug to experience any relief from pain; others may require dosing at shorter intervals. Some clinicians, out of an exaggerated concern for the possibility of inducing addiction, tend to prescribe initial doses of opioids that are too small or given too infrequently to alleviate pain and then respond to the patient's continued complaints with an even more exaggerated concern about drug dependence, despite the high probability that the request for more drug is only the expected consequence of the inadequate dosage initially prescribed (*see* Sriwatanakul *et al.*, 1983). It also is important to note that infants and children are probably more apt to receive inadequate treatment for pain than are adults due to communication difficulties, lack of familiarity with appropriate pain assessment methodologies, and inexperience with the use of strong opioids in children. If an illness or procedure causes pain for an adult, there is no reason to assume that it will produce less pain for a child (*see* Yaster and Deshpande, 1988).

Pain of Terminal Illness and Cancer Pain. Opioids are not indicated in all cases of terminal illness, but the analgesia, tranquility, and even the euphoria afforded by the use of opioids can make the final days far less distressing for the patient and family. Although physical dependence and tolerance may develop, this possibility should not in any way prevent physicians from fulfilling their primary obligation to ease the patient's discomfort. The physician should not wait until the pain becomes agonizing; ***no patient should ever wish for death because of a physician's reluctance to use adequate amounts of effective opioids.*** This may sometimes entail the regular use of opioid analgesics in substantial doses. Such patients, while they may be physically dependent, are not "addicts" even though they may need large doses on a regular basis. Physical dependence is not equivalent to addiction (*see* Chapter 24).

Most clinicians who are experienced in the management of chronic pain associated with malignant disease or terminal illness recommend that opioids be administered at sufficiently short, fixed intervals so that pain is continually under control and patients do not dread its return (Foley, 1993). Less drug is needed to prevent the recurrence of pain than to relieve it. Morphine remains the opioid of choice in most of these situations, and the route and dose should be adjusted to the needs of the individual patient. Many clinicians find that oral morphine is adequate in most situations. Sustained-release preparations of oral morphine are now available that can be administered at 8- to 12-hour intervals. Superior control of pain often can be achieved with fewer side effects using the same daily dose; a decrease in the fluctuation of plasma concentrations of morphine may be partially responsible.

Constipation is an exceedingly common problem when opioids are used, and the use of stool softeners and laxatives should be initiated early. Amphetamines have demonstrable mood-elevating and analgesic effects and enhance opioid-induced analgesia. However, not all terminal patients require the euphoriant effects of amphetamine, and some experience side effects, such as anorexia. Controlled studies demonstrate no superiority of oral heroin over oral morphine. Similarly, after adjustment is made for potency, parenteral heroin is not superior to morphine in terms of analgesia, effects on mood, or side effects (*see* Sawynok, 1986). Although tolerance does develop to oral opioids, many patients obtain relief from the same dosage for weeks or months. In cases where one opioid loses effectiveness, switching to another may provide better pain relief. "Cross-tolerance" among opioids exists, but, both clinically and experimentally, cross-tolerance among related μ-receptor agonists is not complete. The reasons for this are unclear, but they may relate to differences between agonists in receptor-binding characteristics and subsequent cellular signaling interactions, as discussed earlier in the chapter.

When opioids and other analgesics are no longer satisfactory, nerve block, chordotomy, or other types of neurosurgical intervention such as neurostimulation may be required if the nature of the disease permits. Epidural or intrathecal administration of opioids may be useful when administration of opioids by usual routes no longer yields adequate relief of pain (*see* above). This technique has been used with ambulatory patients over periods of weeks or months (*see* Gustafsson and Wiesenfeld-Hallin, 1988). Moreover, portable devices have been developed that permit the patient to control the parenteral administration of an opioid while remaining ambulatory (Kerr *et al.*, 1988). These devices use a pump that infuses the drug from a reservoir at a rate that can be tailored to the needs of the patient, and they include mechanisms to limit dosage and/or allow the patient to self-administer an additional "rescue" dose if there is a transient change in the intensity of pain.

Nonanalgesic Therapeutic Uses of Opioids. ***Dyspnea.*** Morphine is used to alleviate the dyspnea of acute left ventricular failure and pulmonary edema, and the response to intravenous morphine may be dramatic. The mechanism underlying this relief still is not clear. It may involve an alteration of the patient's reaction to impaired respiratory function and an indirect reduction of the work of the heart due to reduced fear and apprehension. However, it is more probable that the major benefit is due to cardiovascular effects, such as decreased peripheral resistance and an increased capacity of the peripheral and splanchnic vascular compartments (*see* Vismara *et al.*, 1976). Nitroglycerin, which also causes vasodilation, may be superior to morphine in this condition (*see* Hoffman and Reynolds, 1987). In patients with normal blood gases but severe breathlessness due to chronic obstruction of airflow ("pink puffers"), *drocode* (dihydrocodeine), 15 mg orally before exercise, reduces the feeling of breathlessness and increases exercise tolerance (Johnson *et al.*, 1983). Opioids are relatively contraindicated in pulmonary edema due to respiratory irritants unless severe pain also is present; relative contraindications to the use of histamine-releasing opioids in asthma already have been discussed.

Special Anesthesia. High doses of morphine or other opioids have been used as the primary anesthetic agents in certain surgical procedures. Although respiration is so depressed that physical assistance is required, patients can retain consciousness (*see* Chapter 14).

PROSPECTUS

Great strides are being made in understanding structure-function relationships between opioids and endogenous opioid peptides and their receptors. The complex signaling mechanisms and neural circuitry mediating both the salutary and undesirable effects of opioids also are beginning to be understood. The recent discovery of new μ receptor-selective endogenous opioid ligands and the opioid-related N/OFQ system also will provide opportunities to improve our understanding of opioid pharmacology and physiology. The development of new opioid analgesics and novel delivery routes are improving the care and quality of life for patients requiring opioids. Over the next several years, pursuing these lines of basic and clinical investigation should provide many valuable insights that may allow better targeting of the therapeutic effects of opioid compounds, thereby minimizing undesirable acute side effects and the potentially serious long-term consequences of tolerance and physical dependence. It also is hoped that these efforts will help overcome the less common, but devastating, problem of addiction.

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Dedication

The authors would like to dedicate this chapter to the memory of Dr. Thomas F. Burks, colleague and friend, who had a major impact on the field of opioid pharmacology.